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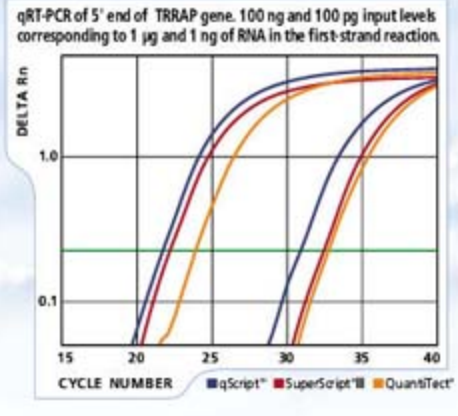


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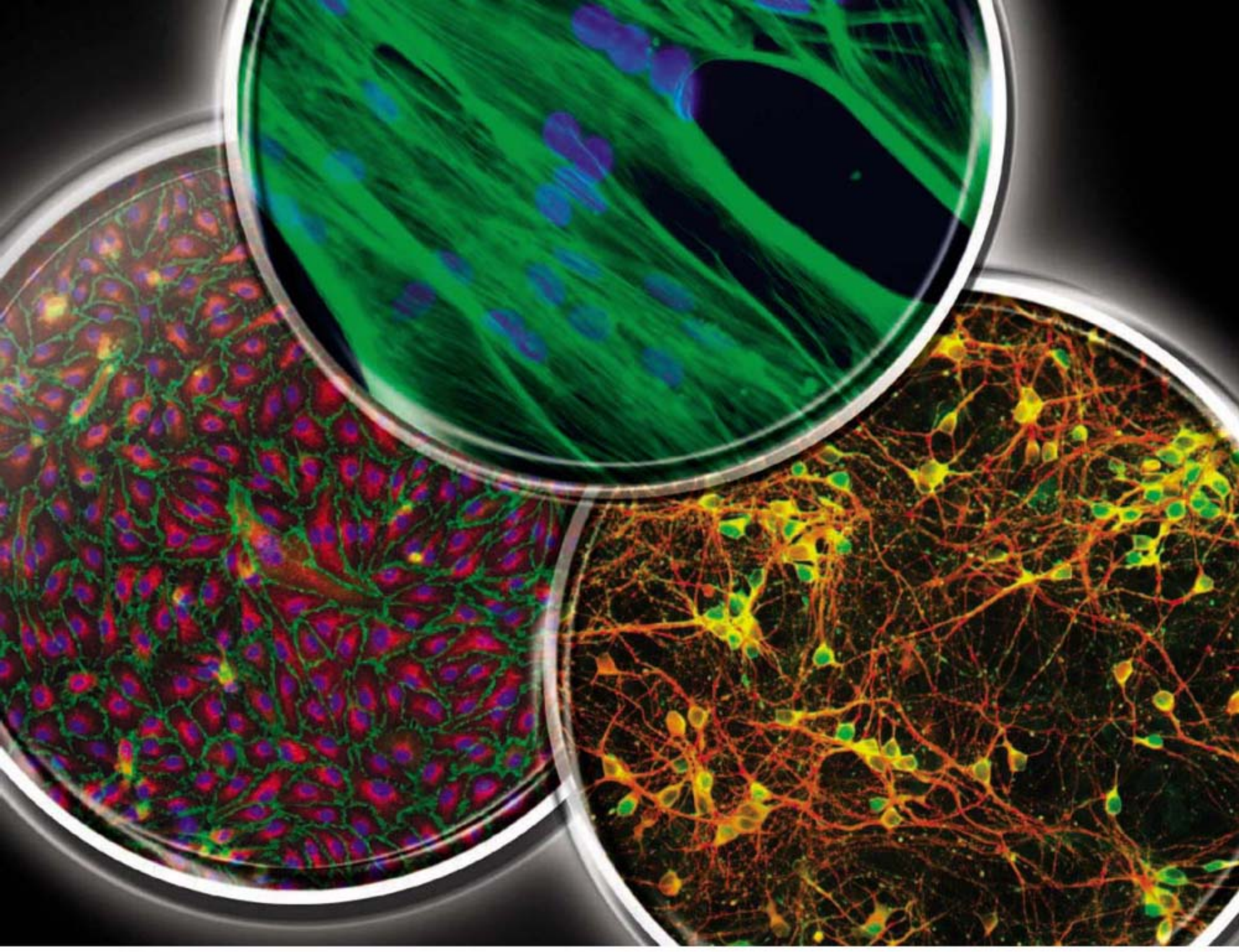

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Volume 317, Issue 5843


## COVER

Person-to-person and, in recent years, person-to-computer interactions shape our worlds. By examining human behavior both in the real and cyber dimensions, and by studying primates in natural settings, researchers are exploring the many aspects of social cognition and its evolution. A special section on social cognition begins on page 1337.

***Photo: Getty Images***

## DEPARTMENTS



## EDITORIAL



SPECIAL SECTION

# Social Cognition

## INTRODUCTION



## NEWS



## REVIEWS



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*For related online content and Podcast, go to www.sciencemag.org/sciext/socialcognition/*



## NEWS OF THE WEEK



## NEWS FOCUS



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MEDICINE

**A Neuroligin-3 Mutation Implicated in Autism Increases Inhibitory Synaptic Transmission in Mice**
*K. Tabuchi* et al.
A mouse model reveals that a mutation that changes the balance of excitatory and inhibitory synapses affects learning skills, a finding that may help understand autism.
10.1126/science.1146221

DEVELOPMENTAL BIOLOGY

**A Vasculature-Associated Niche for Undifferentiated Spermatogonia in the Mouse Testis**
*S. Yoshida, M. Sukeno, Y. Nabeshima*
Time-lapse imaging reveals that the stem cells that generate sperm are located near blood vessels in the testis of mice, a different organization than in invertebrates.
10.1126/science.1144885

GENOMICS

**A Metagenomic Survey of Microbes in Honey Bee Colony Collapse Disorder**
*D. L. Cox-Foster* et al.
A comparative genomic approach suggests that a virus may be contributing to the current devastation of domesticated bee colonies.
*>> News story p. 1304*
10.1126/science.1146498

## LETTERS



## BOOKS *ET AL.*



## POLICY FORUM



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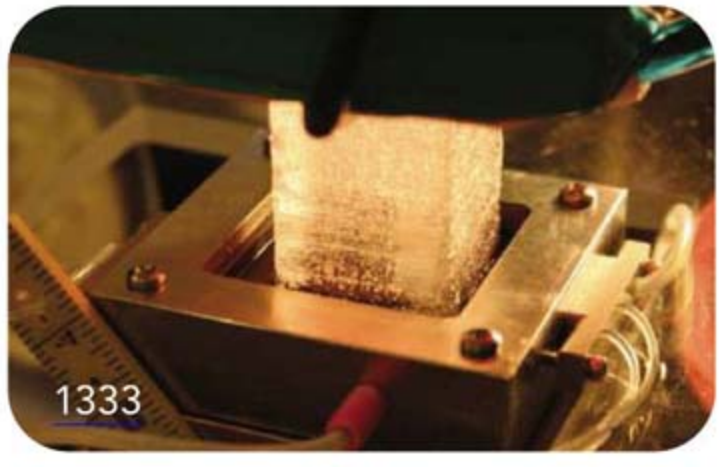


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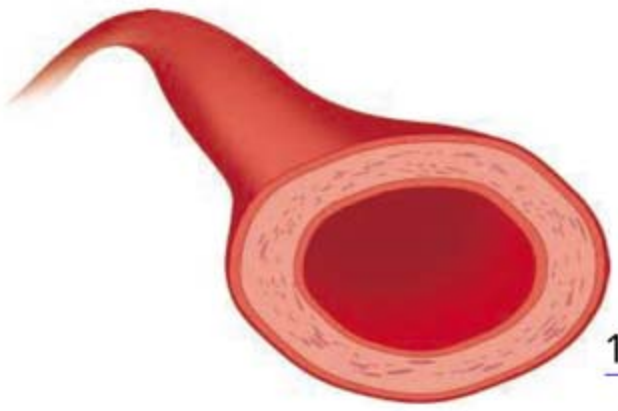
## REPORTS





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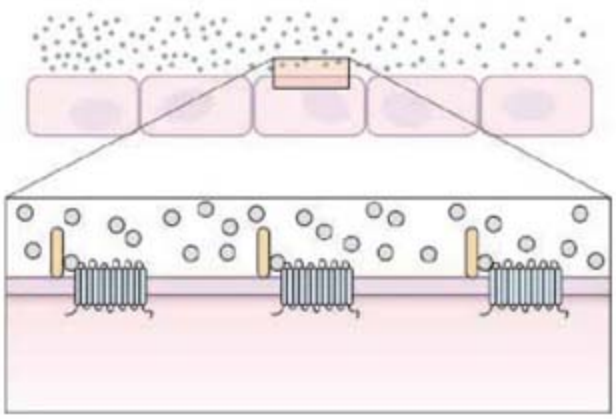
**How the Elderly Stay Positive**
With age, the brain's response to negative emotions may wane.

**Fertile Times for May-December Couples**
Older men who mate with younger women have evolutionary advantage.

**Right Time, Wrong Fish**
Decades of conservation work in Colorado foiled by case of mistaken identity.



Responding to hedgehog.

## SCIENCE'S **STKE**

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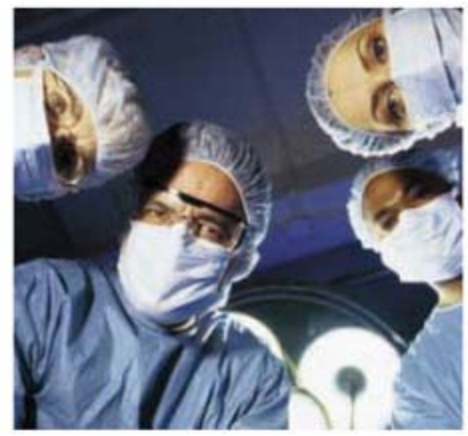
**PERSPECTIVE: The Aryl Hydrocarbon Receptor—An Illuminating Effector of the UVB Response**
*P. Agostinis, M. Garmyn, A. Van Laethem*
The cellular response to ultraviolet B radiation is mediated by the aryl hydrocarbon receptor.

**PERSPECTIVE: Hedgehog Signaling—Cooking with Gas1**
*J.-S. Kang, W. Zhang, R. S. Krauss*
Positively and negatively acting ligand-binding proteins fine-tune the response to hedgehog signaling.



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*B. Benderly*
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**EUROPE: A Karolinska Doctoral Candidate Learns the Joys of Business Ownership, Research, and Fatherhood**
*L. Laursen*
Mohammed Homman is in no hurry to defend his dissertation; he's got other priorities.

**EUROPE: A Job in the Video-Game Industry**
*E. Pain*
As a child, computer scientist Ronan Marchalot played video games, but now he writes them.

**GRANTSNET: September 2007 Funding News**
*GrantsNet Staff*
Learn about the latest in research funding opportunities, scholarships, fellowships, and internships.

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Download the 7 September *Science* Podcast to hear about social cognition in humans and primates, insights into early flight from a small dinosaur specimen, efforts to save China's tigers, and more.
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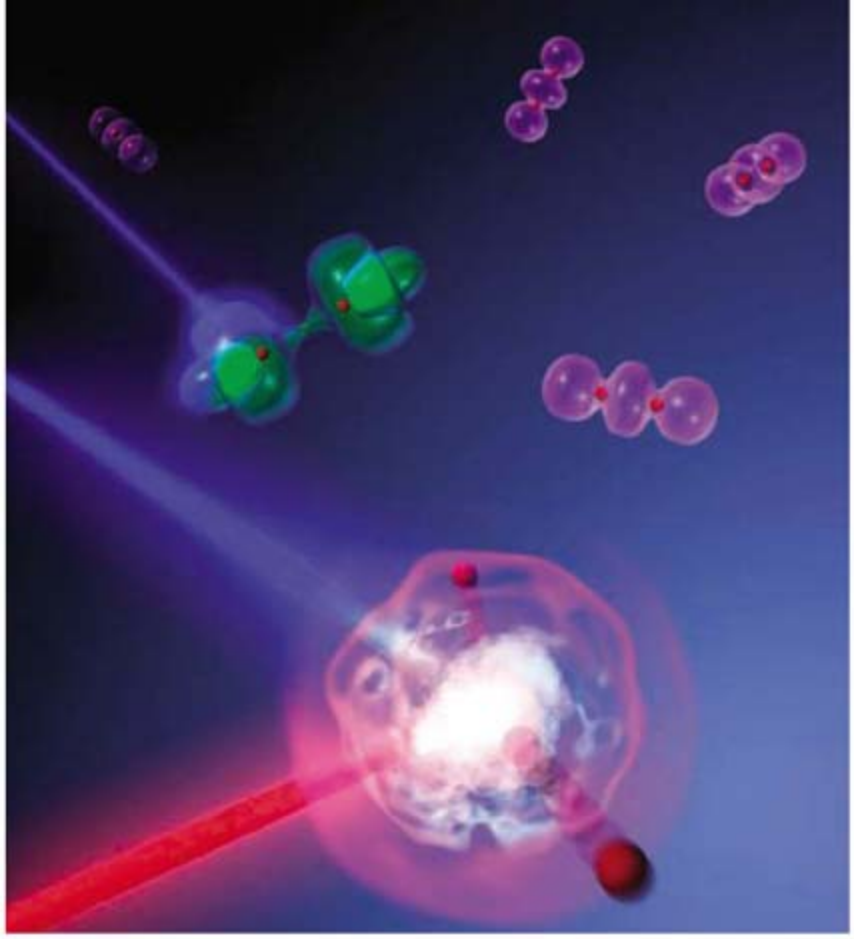


## << Initial Events in X-ray Excitation

X-ray methods have enabled atomic-scale structural characterization of many systems, but the high energy of x-rays can induce chemical damage. Such damage is challenging to probe because the seminal events occur on time scales much shorter than the duration of technologically accessible x-ray pulses. The recent advent of laser-induced high harmonic generation has overcome this limitation, and **Gagnon *et al.*** (p. 1374) apply the technique to study the interaction dynamics of $N_2$ molecules with femtosecond x-ray pulses. The pulses have sufficient energy to eject an electron and simultaneously excite an additional electron in the same molecule, which leads to shell rearrangements on an ultrafast time scale that the authors could characterize through imaging of further ionization events.

## Quantum Criticality in Helium Bilayers

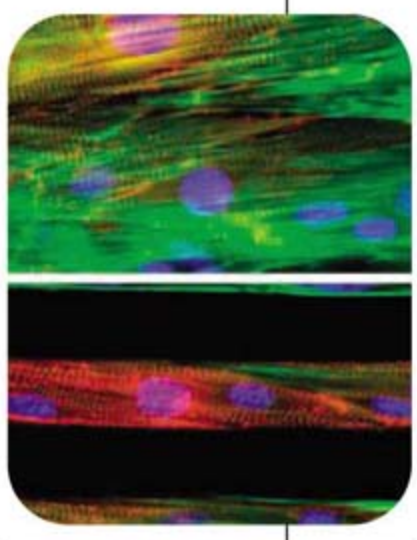
Unlike classical critical points, quantum critical points occur in the limit of zero temperature, where two possible ground states of the system compete as a function of some other system parameter, such as pressure or magnetic field. Quantum criticality is thought to hold the key to understanding the states of matter that do not conform to the "standard model" of condensed-matter physics, Landau Fermi liquid theory. Historically, bulk liquid $^3$He, the simplest Fermi system, played a key role in the development of Landau's theory. However, **Neumann *et al.*** (p. 1356, published online 26 July; see the Perspective by **Hooley and Mackenzie**) show that bilayers of $^3$He show quantum critical behavior when the coverage reaches a critical density. Finding a $^3$He analog of behavior more commonly associated with complex materials may provide a more theoretically tractable system for studying quantum criticality.

## Reassessing Core Spinning

Saturn's rocky core spins hidden beneath thick cloud layers. By combining Cassini gravity measurements with Pioneer and Voyager radio occultation and wind data, **Anderson and Schubert** (p. 1384; see the Perspective by **Podolak**) deduce that Saturn's core rotates 7 minutes faster than the rate determined from previous estimates based on periodicities in magnetic and low-frequency radio data that were not tied directly to the actual motion of the core. Relative to the fast spinning core, our perspective of Saturn's atmospheric winds must also be altered. Much slower eastern wind speeds are needed at the equator, corresponding to a reduced equatorial bulge from 122 to 10 kilometers, and the winds at higher latitudes flow both east and west, as on Jupiter. The more rapid rotation implies a relatively small ice-rock-metal core at Saturn's center.

## Flexible Force Generation

As a compact source of motive power, muscle cells retain many advantages over artificial systems they have inspired; for example, the force delivered and the frequency at which muscle contraction occurs can be tailored over a wide range. However, taking full advantage of muscle cells in devices requires the ability to mimic the three-dimensional nature of muscle tissue starting. **Feinberg *et al.*** (p. 1366) have cultured neonatal rat ventricular cardiomyocytes onto polydimethylsiloxane (PDMS) films on the centimeter size scale. Prepatterning of the support with microcontact-printed lines of fibronectin controlled the tissue shape, and PDMS film thickness controlled the bending stiffness. In this way, complex shapes, such as the spiral form of a mailing tube, could be created. Small devices, which can contract spontaneously or be paced by an external potential, were able to swim, walk, or grip objects.



CREDITS (TOP TO BOTTOM): GREG KEUBLER/UNIVERSITY OF COLORADO; FEINBERG ET AL.

## Clues to Body Sizes of Bird Ancestors

The changes involved in the early evolution of birds and flight (before *Archaeopteryx* appeared in the Jurassic) are poorly preserved in the fossil record. **Turner *et al.*** (p. 1378) describe a later Cretaceous dinosaur from Mongolia that retains many primitive features and is phylogenetically positioned as a basal dromaeosaurid (which are part of the clade Paraves that also includes *Archaeopteryx* and later birds). The taxon's small body size (70 centimeters) supports the notion that a decrease in body size in dinosaurs preceded the evolution of flight in the lineage that led to birds; the largest *Archaeopteryx* is about 65 centimeters.

## Reflections on Sooty Surfaces

Black carbon, or "soot," can impact climate through its extremely efficient absorption of sunlight. Although most of the impact of soot comes from its presence in the atmosphere, its influence can be critical when it deposits on snow and ice and dramatically changes surface reflectivity. **McConnell *et al.*** (p. 1381, see the Perspective by **Alley**; published online 9 August) present a 215-year-long record of North American emissions of black carbon, based on its concentration in an ice core from Greenland. Black carbon deposition was greatest between about 1850 and 1950, and industrial activity

*Continued on page 1291*

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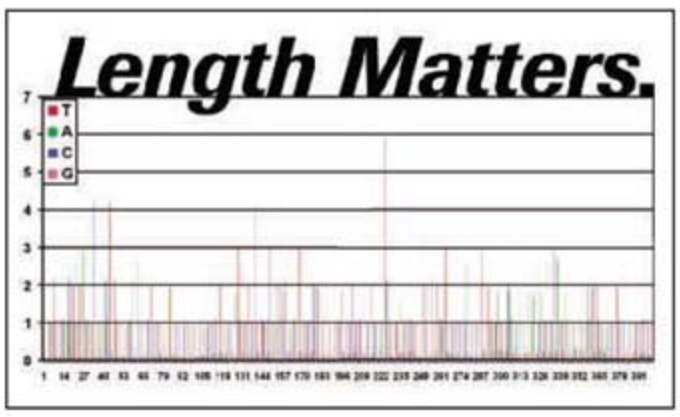


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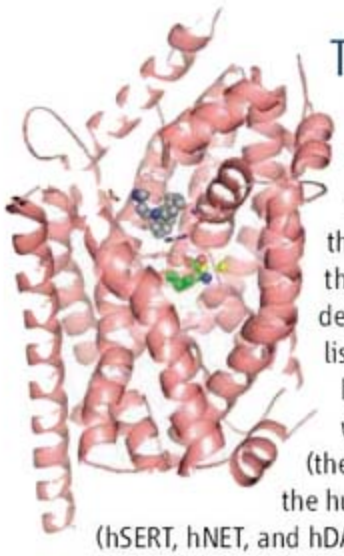
*Continued from page 1289*

during that period resulted in an increase of radiative forcing at the surface as much as eight times greater than that during the preindustrial era.

## Acquiring the Necessary Skills

Humans are social animals and, aided in large part by language, are supremely capable of transferring knowledge and skills across generational and genetic boundaries. One way to gain insight into how these social cognitive skills arose is to detect differences in the onset of some of these skills in human, ape, and monkey infants. **Herrmann *et al.*** (p. 1360) present the implementation of what they have labeled the Primate Cognition Test Battery, which has been designed to assess social and physical cognition, in approximately 100 children, 100 chimpanzees, and 30 orangutans. At an age of 2½ years, human children perform as well as chimpanzees on the physical tasks and much better than them on social tasks. Human adults normally use their hands, not their heads, to turn a light switch. So do infants, even after they have observed an adult using their head—if they see that their hands were occupied by holding a blanket. However, if infants see an adult use their head when their hands are free, they conclude that there must be some underlying reason for using the head, and they will do so, too. **Wood *et al.*** (p. 1402; see the news story by **Pennisi**) assess whether this capacity for looking beyond the surface to see the intentions underlying goal-directed actions can be detected in nonhuman primates. They find that it can—in chimpanzees, macaques, and tamarins—implying that bases for this cognitive skill arose at least 40 million years ago.



## The Molecular Machinery of Mood Swings

The action of monoamine neurotransmitters that serve as signaling molecules in mood and motivation begins when they are released from the presynaptic nerve terminal and ends when they are transported from the extracellular space back into the cytoplasm via dedicated sodium-dependent plasma membrane transporters. **Zhou *et al.*** (p. 1390, published online 9 August) describe the crystal structure of a bacterial homolog (LeuT) of the mammalian monoamine transporters in complex with its substrate (leucine) and an inhibitor of norepinephrine transport (the antidepressant desipramine). On the basis of homology modeling of the human transporters for serotonin, norepinephrine, and dopamine (hSERT, hNET, and hDAT), they construct mutants of hSERT and hDAT and show that these exhibit the predicted sensitivity of serotonin and dopamine uptake to desipramine inhibition.

## Genetic Risks in Exfoliation Glaucoma

Exfoliation glaucoma (XFG) is a common, sight-threatening disease associated with chronic accumulation of fibrillar matrix products caused by abnormal aggregation of elastic microfibril components (exfoliation syndrome). **Thorliefsson *et al.*** (p. 1397, published online 9 August; see the 10 August news story by **Marx**) performed a whole-genome association study on an Icelandic cohort and a Swedish cohort and found that XFG was associated with variation in the *LOXL1* gene, a member of the lysyl oxidase family of proteins, that is involved in the formation of the elastin polymer fibers. Two common single nucleotide polymorphisms (SNPs) that result in changes in the region of the protein that affects substrate specificity were identified that were associated with the exfoliation syndrome and with XFG. The risk for XFG that they confer on those who have two copies of the high-risk haplotype of the two SNPs is more than 100 times greater than that for those with only the low-risk haplotypes.

## A Genetic Handle on Head Blight

*Fusarium graminearum*, a fungal plant pathogen that causes head blight of wheat and barley, has resulted in the largest economic loss to United States agriculture in the last decade. **Cuomo *et al.*** (p. 1400) sequenced the genome of *F. graminearum* and revealed genes involved in host-pathogen interactions. In addition to the genome sequence, more than 10,000 single nucleotide polymorphisms were identified through comparison with a sequence from a second strain. These data suggest that within the genome, highly variable and gene-rich regions harbor genes potentially associated with pathogenicity.

CREDIT: ZHOU *ET AL.*

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John T. Bruer is president of the James S. McDonnell Foundation, St. Louis, MO 63117, USA. E-mail: bruer@jsmf.org

# The Brain/Education Barrier

IN AN ERA OF TRANSLATIONAL SCIENCE, RESEARCHERS OFTEN FIND THEMSELVES IN THE mixed company of policy-makers, legislators, and educators looking for "evidence-based" practice. That's how it was earlier this year in March, when a distinguished international group of neuroscientists and cognitive psychologists convened at the University of Chile in Santiago for the conference titled Early Education and Human Brain Development, which many Chilean ministers, educators, and scientists attended to learn how brain science might transform education. On day one, however, it became clear that myths about brain-based pedagogy dominated participants' thinking. The Chilean educators were looking to brain science for insights about which type of preschool would be the most effective, whether children are safe in child care, and how best to teach reading. The brain research presented at the conference that day was mute on these issues. However, cognitive and behavioral science could help.

How could an international group of scientists communicate that there is superb developmental evidence that speaks directly to educational concerns, whereas brain science cannot yet do so? How might brain science become an aspect, rather than the driving force, of ongoing educational discussions? To address these questions, we and scientists from Chile, France, Germany, Holland, Spain, the United Kingdom, and the United States drafted the Santiago Declaration, a statement reflecting what science can tell us about early education. It summarizes knowledge about child development and early learning, the benefits of embedding learning in meaningful social contexts, the importance of active rather than passive learning, the need for sensitive and responsive environments, and the need for concern about how, not just what, children learn. We hope that this declaration (www.jsmf.org/declaration) will become a focal point for the discussion of evidence-based educational practice.

How did the myth of brain-based pedagogy become so pervasive in educational discussions? How did policy-makers, educators, and the public become so misinformed? Current worldwide interest in early childhood development can be attributed to a successful public relations campaign launched in the mid-1990s in the United States. The campaign promoted legislation to fund Early Head Start. Media interest made the campaign's message headline news for parents around the world. Yet brain science, which is still refining methods to analyze early brain development, is not ready to relate neuronal processes to classroom outcomes.

Current brain research offers a promissory note for a future in which developmental models and theories of learning may be refined based on how brain systems support learning. Meanwhile, popular misunderstandings present a serious downside. One example is the emphasis given to the popular, but scientifically unsupported, notion of a critical period during which children's brains can learn almost any subject efficiently. Belief in a biologically limited critical period for learning mobilized governments, legislators, and media worldwide to pass legislation and fund early childhood programs. The educational literature is now stocked with books and articles boasting brain-based curricula and practices. Brain-based consultants continue to visit school districts. And a market has grown for brain-based toys. The message of synaptic growth and critical periods has affective appeal, but no scientific substance. Unfortunately, this enthusiasm has caused us to neglect research that tells us how children learn.

The Santiago conference suggested how scientists might better function in mixed translational company. We must keep in mind that motivated educators and policy-makers are the end users of scientific research. Scientists should listen to the practical questions generated by these consumers. Real dialogue starts when we address misconceptions and misunderstandings across the research/practice divide. Over time, these conversations can lead to a common vocabulary, informed engagement, meaningful applied research, and ideally, evidence-based practice. The conversation might even contribute to more informed policy discussions. We applaud the attention directed to the world's youngest citizens, and urge that policies, standards, curricula, and, to the extent possible, commercial ventures, be sensitive to evidence-based practice based on the best scientific research.

**– Kathryn Hirsh-Pasek and John T. Bruer**

10.1126/science.1148983

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ECOLOGY/EVOLUTION

## Globalization via Drift

The evolutionary consequences of plate tectonic movements on biological organisms are often hard to reconstruct. The twin processes of extinction and dispersal tend to obscure biogeographical patterns that might otherwise be interpreted straightforwardly in the context of continental drift. The ideal group of organisms for such a study would be one that is ancient (originating before the breakup of Pangaea roughly 200 million years ago), that disperses poorly or not at all, and that still survives worldwide. Boyer *et al.* have focused on Cyphophthalmi—a suborder of the spiderlike long-legged harvestmen that inhabit leaf litter—which originated around 400 million years ago. A phylogeny constructed from DNA sequence data shows that almost all families of these harvestmen show clear biogeographical patterns that can be traced backward to the breakup and dispersal of the major land masses and continental islands. Relationships between the families suggest that the New Caledonian fauna (Troglosironidae) is more closely related to that of the former Gondwanan tropics (Neogoveidae) than to those of Australia and New Zealand, and this shared origin explains why they both exhibit the unusual row of teeth on the second walking-leg claw. — AMS

*J. Biogeogr.* **34**, 10.1111/j.1365-2699.2007.01755.x (2007).

CHEMISTRY

## Reduced by the Main Group

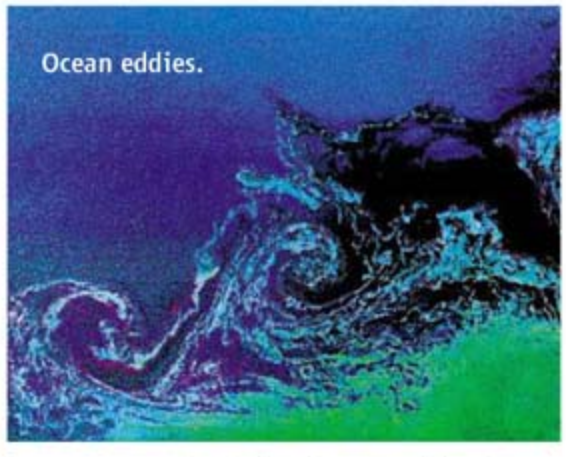
The addition of $H_2$ across C=O and C=N multiple bonds has tended to require help from transition metals to coax the process along by first slicing through the bond connecting the two H atoms. An unusual metal-free complex, composed of phosphorus and boron centers bridged by a fluorinated phenyl ring, was recently also shown to reversibly cleave $H_2$—ostensibly by proton addition to P and hydride transfer to B. Chase *et al.* have now found that, like transition metal complexes, this main group compound acts as an effective catalyst for hydrogenation of CN bonds in aziridines and sterically encumbered imines. The reaction is fastest when electron-donating substituents raise the basicity of the imine nitrogen, implicating a mechanism involving initial proton transfer from the P center. Nitriles and less bulky imines blocked catalysis by coordinating tightly to the B center but could be induced to react through protection by an external coordinating borane. — JSY

*Angew. Chem. Int. Ed.* **46**, 10.1002/anie.200702908 (2007).

OCEAN SCIENCE

## An Emergent Role for Eddies

Much of the kinetic energy of the ocean is concentrated in the mesoscale region of its energy spectrum, which is populated by structures with dimensions of tens to hundreds of kilometers and durations of tens to hundreds of days. There are two distinct types of mesoscale variability—linear westward-propagating Rossby waves and nonlinear eddies—but it is difficult to distinguish one from the other observationally. Satellites have proven to be the best platform for measuring the extent of these features, and based on data they yielded, the accepted view became that most of the mesoscale variability of




the oceans was due to Rossby waves. Now, however, Chelton *et al.* have used additional multisatellite altimeter data to show that more than half of the extratropical sea surface height variability that defines these structures is actually due to eddies. The remaining variation is probably due to eddies with shorter lifetimes, methodological error, and other physical processes such as Rossby waves. Because nonlinear eddies can transport momentum, heat, and mass, they can contribute to general circulation and ocean biology in ways that Rossby waves cannot. — HJS

*Geophys. Res. Lett.* **34**, L15606 (2007).

MOLECULAR BIOLOGY

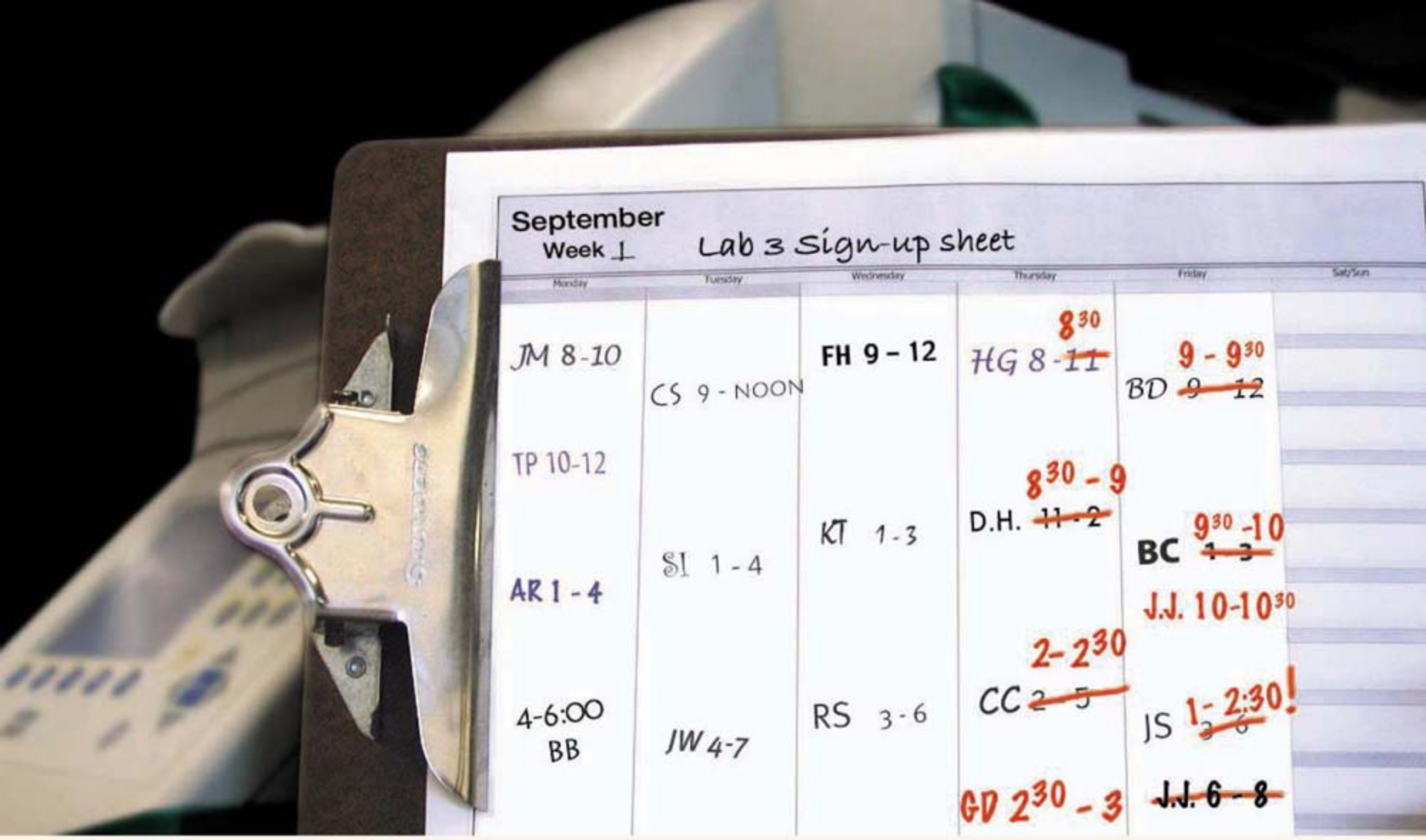
## Prospective Sampling

Like its chemical cousin DNA, the most common structural motif adopted by RNA is the double helix. There are many instances (transcription, pre-mRNA processing, and ribosome biogenesis) where double-stranded RNA (dsRNA) needs to be unwound and unzipped, functions performed by motor proteins known as RNA helicases. To understand more about how helicases go about their business, Cheng *et al.* have challenged the hepatitis C virus NS3 helicase with strong-versus-weak and long-versus-short barriers. They show that NS3 readily unzips a hairpin of 30 A:U base pairs but dissociates or pauses before entering the same length of more stable G:C base pairs. When faced with a three-G:C base pair zipper, NS3 ploughs right on through, yet lengthening the barrier to six G:C base pairs causes NS3 to pause, indicating that the enzyme must be sampling the RNA just ahead of where helicase-mediated unwinding takes place. The former interaction may serve to destabilize the dsRNA during the pause that precedes unwinding and thereby enhance the processivity of the enzyme. — GR

*Proc. Natl. Acad. Sci. U.S.A.* **104**, 13954 (2007).

*Continued on page 1297*

CREDITS (TOP TO BOTTOM): (MAIN) G. GIRIBET; (INSET) BOYER *ET AL.*, *J. BIOGEOGR.* **34**, 10.1111/J.1365-2699.2007.01755.X (2007); JPL/NASA

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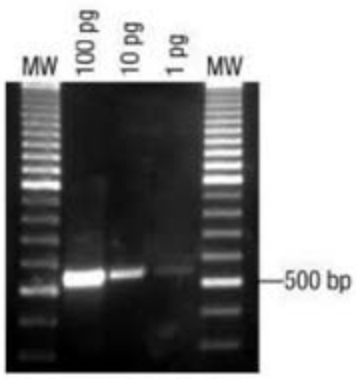


**FIG 1. A 539 bp fragment was amplified from as little as 1 pg of lambda DNA in 16 minutes.**

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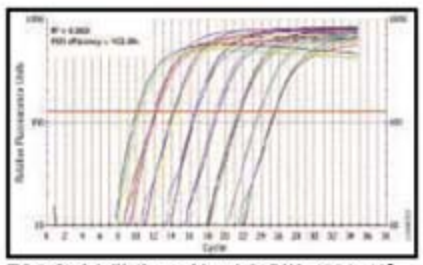

**FIG 2. Serial dilutions of Lambda DNA, 128 to $10^7$ copies, was amplified.**

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*Continued from page 1295*

MATERIALS SCIENCE

## Solidifying into Shape

Finding materials that spontaneously form specific ordered patterns is a key for bottom-up fabrication strategies at the nanometer scale. Block copolymers, in which two or more dissimilar polymers are chemically linked, have the advantage in this respect of being thermodynamically driven toward regularly spaced patterns. One shortcoming though is that tuning the pattern often requires synthesis of a new block copolymer. Ejima *et al.* show that directional crystallization, a technique that has been used to enhance the patterning of block copolymers, can also be applied to a mixture of dissimilar homopolymers, which would normally phase-separate into large disordered regions. They combined poly(L-lactic acid) (PLLA), a crystallizable polymer, with poly(vinyl acetate) (PVAc),

one of many amorphous polymers with which PLLA is miscible. The two were dissolved at high temperature in hexamethylbenzene (HMB) and afterward transferred to a heating stage below the melting temperatures of HMB and PLLA but above the glass transition temperatures of both polymers. As the HMB crystallized along a growing front, the concentration of PLLA increased until it too formed axial crystals in the same direction (as distinct from the usual spherulitic morphology). Pitch spacings of 69 nm were observed over large sample areas and were tunable by variation of the PVAc fraction. — MSL

*Macromolecules* **40**, 6445 (2007).

CHEMISTRY

## A New Pair of Dice

The metal-sulfide clusters at the heart of the nitrogenase proteins pose questions for the biochemist—how are these assembled and inserted?—and for the inorganic chemist—what are the electronic properties that enable these enzymes to catalyze the reduction of dinitrogen under mild conditions? The P cluster ($Fe_8S_7$) and the FeMo cofactor ($MoFe_7S_9$) of the MoFe nitrogenase both contain a framework that can be described as two cubes joined at a vertex, which is either a hexacoordinate sulfur atom or an unidentified light atom (thought to be C, N, or O), with the central six iron atoms connected by two or three other sulfur ligands. Ohki *et al.* have synthesized a new [8Fe-7S] cluster where the incomplete cubanes are linked by a hexacoordinate sulfur and three anionic ligands. Bulky thiol substituents (R = dimesitylphenyl and triisopropylphenyl) and nonpolar solvents stabilized the dimeric $[Fe_2(\mu\text{-}SR)_2]$ core of the starting material, which after reaction with elemental sulfur for 4 days provided a $Fe_8S_7$ cluster in 28% yield. A cyclic voltammogram indicated that the cluster may be electrochemically active, and EPR measurements supported the assignment of the oxidation states as $Fe(II)_5Fe(III)_3$. The P cluster and the FeMo cofactor are but a few synthetic steps away, at least on paper, raising the possibility that this thermodynamically stable construct might also be accessed biochemically. — GJC

*J. Am. Chem. Soc.* **129**, 10457 (2007).

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## << A Silent Partner

Like the vertebrate retinoid X receptors (RXRs) that it structurally and functionally resembles, the arthropod protein ultraspiracle (USP) heterodimerizes with other nuclear receptors to activate transcription of target genes. Various substances activate RXRs and have been postulated to serve as endogenous ligands, and the USP binding partner EcR (ecdysone receptor) is activated by ecdysone. Noting the similarity between the ligand-binding domain of USP in arthropods that are not Mecopterida (which includes the flies and moths) to that of the RXR, Iwema *et al.* cloned USP from the beetle *Tribolium castaneum* (TcUSP) as a representative non-Mecopterida USP. RXR ligands failed to activate a protein containing the TcUSP D/E domains (regions important for ligand binding and heterodimerization), and electrospray ionization mass spectrometric analysis indicated that TcUSP failed to bind RXR ligands in vitro. Analysis of the crystal structure of the TcUSP ligand-binding domain in the context of a functional TcUSP-EcR heterodimer indicated that TcUSP exhibited a stable apo structure in an inactive antagonist conformation, which did not have a conventional ligand-binding pocket. Phylogenetic analysis emphasized the evolutionary plasticity of the RXR-USP–family ligand-binding domain, suggesting that even though non-Mecopterida USP does not, RXRs do indeed bind endogenous ligands. — EMA

*EMBO J.* **26**, 3770 (2007).

CREDIT: ADAPTED FROM E. JIMA *ET AL.*, *MACROMOLECULES* **40**, 6445 (2007)

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See pages 120 and 121 of the 5 January 2007 issue or access www.sciencemag.org/feature/contribinfo/home.shtml

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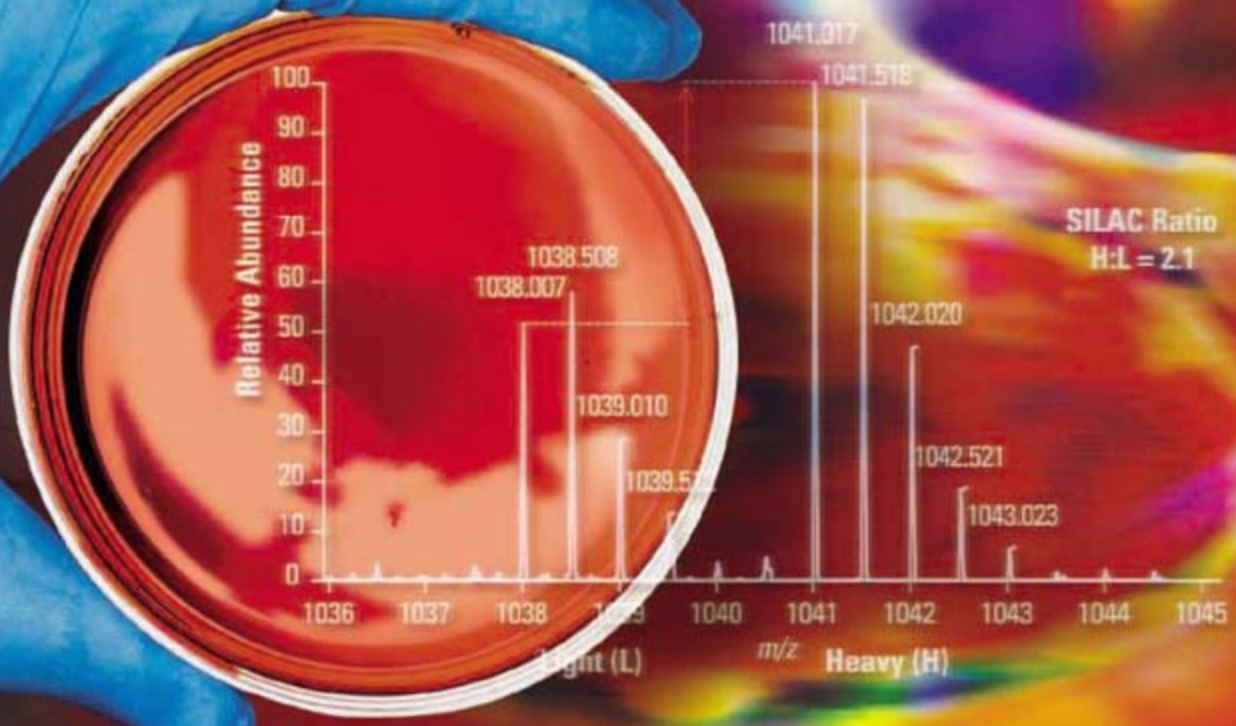


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# Born to Shop?

Women have an evolved knack for remembering where to find edible plant matter, a new study argues.

Rafts of studies have shown that men trump women at many spatial skills, a spillover from our past, say evolutionary psychologists, when men were the hunters and women the gatherers. Studies have also shown that women beat out men in recalling objects' locations. But no one had tested this skill with foods.

So a team led by Steven Gaulin of the University of California (UC), Santa Barbara, tested modern city dwellers on the closest thing to foraging: browsing in a farmers' market. After looking around the stalls, the 86 subjects were asked to remember where they'd seen particular foods. The test involved dead reckoning, a male-dominated skill, rather than navigating by landmarks, a female forte. Yet women were 27% more accurate than men in recalling food locations, the scientists reported online 21 August in the *Proceedings of the Royal Society B*.

"The results fit well with the foraging adaptation theory that explains why women should perform better than men in such a spatial cognition task," says evolutionary psychologist Andreas Wilke of UC Los Angeles. But he notes that both sexes "were significantly more accurate in locating high-calorie food items," such as avocados and olive oil.

## Lights, Camera, Clarify

NET WATCH

A difficult paper might be easier to grasp if you could get an explanation directly from the authors. That's the premise behind SciVee, a new video-sharing site from the Public Library of Science, the National Science Foundation, and the San Diego Supercomputer Center.

Part YouTube, part seminar series, SciVee allows researchers to post short videos, or pubcasts, in which they explicate their latest papers. The offerings explore a technique for identifying bendable sections of proteins and follow an evolutionary analysis of the protein kinase–like superfamily, which is involved in everything from cell division to fat breakdown. For newbies, the site offers advice on video production and posting. So far, SciVee's focus is open-access papers in biology, but it will expand to include other subjects and types of publications. >>
www.scivee.tv

## Last Word on Moths

A Cambridge University professor has completed a 6-year experiment with peppered moths that he says should conclusively rebut creationist claims.

The story of Britain's peppered moth has long been a textbook illustration for evolution by natural selection. The pale moths evolved a black color for camouflage against predators as industrial pollution darkened the trees they rested on. With pollution cleanup, most of the moths went back to being pale. But creationists have used the tale to attack evolution because field experiments done in the 1950s by Oxford zoologist Bernard Kettlewell—used to illustrate the textbooks—were flawed, in part because he released the night-flying moths during the daytime.

So in 2000, geneticist Michael Majerus started his own experiment (*Science*, 25 June 2004, p. 1894). He released black or white moths into cylindrical cages on branches at dusk. Before dawn, he removed the cages and counted how many moths subsequently disappeared from their resting places. He showed that selection now favors pale moths, with 21% eaten by birds, compared with 29% of the black ones, he reported last week at a meeting of the European Society for Evolutionary Biology in Uppsala, Sweden.

**White peppered moth almost impossible to spot (*arrow*).**

Will that take any wind out of creationists' sails? "It's probably not going to quiet them down," says peppered moth expert Bruce Grant of the College of William and Mary in Williamsburg, Virginia, who points out that the evidence for natural selection in the moths was firmly in place long before Kettlewell came along with his vivid photographs.

## DEBUGGING JAPAN'S CABLES

Surprising—and unwelcome—customers have been taking advantage of Japan's high-speed optical fiber communications services. Cicadas have been laying eggs in the cables, which connect homes to main lines, cutting the optical fibers in the process.

Astonished engineers at Nippon Telegraph and Telephone Corp. (NTT) have blamed the loss of service—more than 1000 cases last year—on an infestation of *Cryptotympana facialis*, known as "kumazemi" or "bear cicada." Hideharu Numata, an entomologist at Osaka City University who is advising the phone company, says 7-centimeter-long kumazemi are proliferating in urban areas.

**Caught in the act.**

The fiber-optic cables are "a little thinner than the preferred dead twigs but still okay" from the bugs' perspective, he says, adding that the hair-thin optical fibers sheathed in soft polyethylene sleeves are no match for the bug's tough millimeter-wide, centimeter-long ovipositor.

NTT has improved shielding on its new cables and is trying a polyurethane coating thought to be more like the bark of a live twig, which the cicadas avoid. "It's not clear yet whether this problem can be so easily fixed," Numata says.

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# Celebrities

**OUT OF AFRICA.** The biggest star in Houston, Texas, these days is a 3.2-million-year-old hominid from Ethiopia. The famous fossil, named Lucy, is at the center of a controversial exhibition at the Houston Museum of Natural Science. Advance tickets were selling briskly at up to $20 for the show, which opened last Friday.

Lucy has never been displayed outside Ethiopia since her discovery in 1974. But now she's on a 6-year tour of the United States that Ethiopian tourism officials hope will generate millions for the country. Many paleoanthropologists are protesting the tour, arguing that it could damage the fragile, one-of-a-kind fossil (*Science*, 27 October 2006, p. 574).

Houston is her only announced destination, although officials at the Field Museum of Natural History in Chicago, Illinois, have "tentatively scheduled" the Lucy exhibit from November 2009 to April 2010. Other museums, such as the Smithsonian National Museum of Natural History in Washington, D.C., and the Cleveland Museum of Natural History in Ohio, have refused to exhibit her. Houston museum officials say she's in good hands, pointing to their safe stewardship of precious artifacts such as the Dead Sea Scrolls.

## IN BRIEF

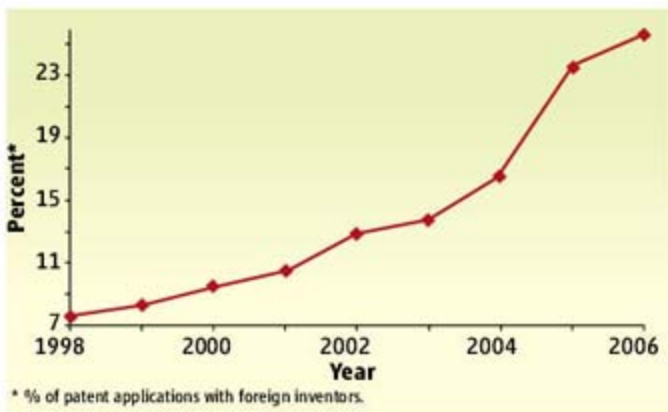
**Nancy Andrews** has been appointed dean of the Duke University School of Medicine in Durham, North Carolina. A pediatric hematologist/oncologist, Andrews has served as dean of basic sciences and graduate studies at Harvard Medical School since 2003. She will be the first woman to lead the Duke school.

**Richard Hodges** is the new director of the University of Pennsylvania Museum of Archaeology and Anthropology. An early medieval archaeologist who specializes in Western Europe, Hodges comes to Penn from the University of East Anglia in the U.K., where he has been directing the Institute of World Archaeology.

## DATA POINT

**DRIVING THE ECONOMY.** Foreign scientists and engineers working in the United States constitute a growing share of the country's innovation capital. Last year, that pool of talent contributed to 26% of U.S. patent applications filed with the World Intellectual Property Organization (WIPO). That's over three times more than their percentage in 1998, an explosion likely triggered by increased delays in the awarding of green cards and citizenship to immigrant scientists, according to researchers who did the study (www.globalizationresearch.com).

Vivek Wadhwa, a researcher at Duke University in Durham, North Carolina, and his colleagues counted up the share of patent applications filed at WIPO's U.S. office that listed a U.S.–based foreign national as one of the inventors. In another part of the study, the researchers estimate that more than 1 million foreign-born workers are waiting for employment-based green cards. "There are a lot of very bright people that we brought to the U.S. in order to create intellectual property," says Wadhwa. "Let's keep them."

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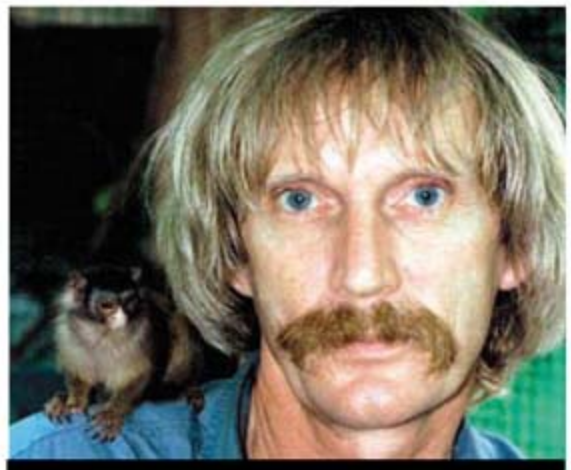


## Three Q's >>

Dutch-born primatologist **Marc van Roosmalen**—a 2000 *Time* magazine "Hero for the Planet"—has discovered five new monkey species during a career exploring the Amazon rain forest. But in June, a Brazilian court found him guilty of violating several laws, including keeping endangered monkeys in a halfway house and putting the names of newly discovered species up for sale. Van Roosmalen, 60, was released on 7 August while a new legal team appeals the decision, which carries a 14-year prison sentence.

**Q: Tell me about your time in jail.**

It was a crazy and eye-opening experience. I was locked up with dangerous criminals who were literally killing each other. I couldn't communicate with the outside world; I couldn't sleep. A survival instinct kicked in.

**Q: What has happened since your release?**

It's like a John Grisham novel. Within 30 hours, two men pretending to be federal police came to my house [in Manaus]. I'm sure they were hit men. Fortunately, I wasn't home, and I've been on the run since then. I have seen too many examples of corruption during my years in the Amazon. I have written everything down and sent it to people in the Netherlands so that the world will know even if something happens to me.

**Q: How has the scientific community reacted?**

Brazilian scientists have supported me. They realize that the government is criminalizing biological research and that this could happen to them. But I think everything will be okay in the end. I'm 100% innocent.

CREDITS (TOP TO BOTTOM): COURTESY OF THE HOUSTON MUSEUM OF NATURAL SCIENCE; ERALDO PERES/AP PHOTO

Fallout from an asteroid smashup 1310

Venter's genome 1311

GENOMICS

# Puzzling Decline of U.S. Bees Linked to Virus From Australia

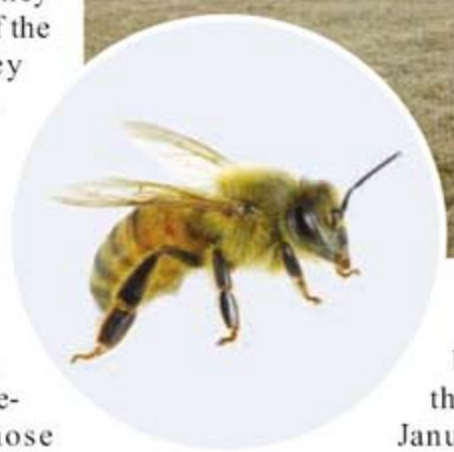
Researchers have found an imported virus that may be associated with the sudden disappearance of honey bees in the United States, known as colony collapse disorder (CCD). This baffling syndrome, which earlier this year made headlines around the world, may have afflicted as many as 23% of beekeepers in the United States and caused losses of up to 90% of hives in some apiaries. The identification of a suspect is an important step, says Nicholas Calderone of Cornell University. "Before, we didn't even have circumstantial evidence."

The suspect is a pathogen called Israel acute paralysis virus (IAPV). A team of researchers reports online in *Science* this week (www.sciencemag.org/cgi/content/abstract/1146498)that they found the virus in most of the affected colonies they tested, but in almost no healthy ones. If the virus proves to be the cause of CCD, it could have international economic implications, for the researchers point to Australia as a possible source. Since 2005, U.S. beekeepers, especially those struggling to keep up with the insatiable demand for almond pollination in California, have imported several million dollars' worth of bees from Australia. The researchers report that they have found IAPV in imported Australian bees.

The investigation is still in an early stage, and there are skeptics. Another group has not found any link between IAPV and CCD. "This paper only adds further to the confusion surrounding CCD," argues Denis Anderson, an entomologist with the Australian Commonwealth Scientific and Industrial Research Organisation (CSIRO) in Canberra, who has not participated in either group.

The abrupt loss of bee colonies in the United States, first reported last fall, has been a big mystery. Although some scientists aren't convinced that the phenomenon—based largely on anecdotal reports from beekeepers—is really any different from past declines in bee populations (*Science*, 18 May, p. 970), bee researchers from around the country met in Florida in January and formed a working group to track down the culprit. The co-chairs, entomologists Diana Cox-Foster of Pennsylvania State University in State College and Jeffery Pettis of the U.S. Department of Agriculture's Bee Research Laboratory in Beltsville, Maryland, acquired samples from collapsed colonies and asked molecular biologist W. Ian Lipkin of Columbia University's Mailman School of Public Health to help in the search for pathogens.

**Hazardous import?** The sudden loss of honey bees, particularly among trucked hives, has been linked to a virus that may have arrived with bees from Australia.



Lipkin initially pooled samples from four beekeeping operations that had been struck with CCD and, for comparison, he lumped together samples from two operations that had remained healthy. When the group ran the samples through a gene sequencer, they found an array of microorganisms. All the bees had a rogue's gallery of pathogens, but the samples from the CCD operations tended to be more disease-ridden, with two viruses and two microsporidian parasites especially prevalent.

Next, the team went back and analyzed samples from individual hives. IAPV turned up in 25 of the 30 sick colonies but in just one of the 21 healthy colonies. "It's a good marker," says Mady Hornig of Columbia University. Others note, however, that bees in hives suffering from CCD tend to accumulate all sorts of secondary diseases, so IAPV infection could be a consequence rather than a cause of the disorder. "It's a chicken-and-egg problem," says bee virologist Joachim de Miranda of the Sveriges Lantbruksuniversitet in Uppsala, Sweden.

Jerry Bromenshenk of Bee Alert Technology in Missoula, Montana, doubts the link to CCD. His collaborators at the U.S. Army's Edgewood Chemical Biological Center in Maryland have spotted more than a dozen known and new viruses, including IAPV, in bees from Florida, California, and Australia, but none is associated with CCD. "We've got lots of pathogens but no clear pattern yet," Bromenshenk says.

Evidence in the paper points to Australia as the source of IAPV. All of the operations infected with IAPV had either imported bees from Australia or stored their hives close to other operations with Australian bees. None of the CCD-free beekeepers, located in Hawaii and Pennsylvania, had Australian bees. Moreover, the team ordered bees from Australia and discovered IAPV in most of them. Samples of bees collected in Pennsylvania and Louisiana in 2004—before the importation of bees began—turned out negative.

But some researchers point out that this limited testing doesn't rule out the

CREDITS (LEFT TO RIGHT): DAN FARRALL/GETTY IMAGES; WIKIPEDIA

Breeding controversy
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DNA duplication and disease
1315

possibility that IAPV may have already been in the country before U.S. beekeepers began importing Australian bees. And Anderson notes that IAPV does not seem to be causing harm in Australia.

Ilan Sela, a plant virologist at the Hebrew University of Jerusalem who first isolated IAPV in 2002 from dead bees taken from Israeli colonies, says IAPV is far from harmless. In experiments reported in the 5 June issue of *Virology*, Sela and colleagues show that, when injected, IAPV causes paralysis and death in 98% of bees within days. If fed to the bees, they survive just a few days longer. "IAPV kills," he says.

So why is there no CCD in Australia, even though IAPV is presumably there? One reason could be that, unlike the United States, Australia remains free of the varroa mite, which spreads pathogens and weakens the immune system of bees. But that can't be the whole story, Pettis notes, because CCD also appears to be absent in Canada and Israel, where varroa mites are a problem and beekeepers have imported Australian bees for years.

Pettis says other stresses in the United States such as poor nutrition and long-distance trucking may make IAPV lethal. Within the next few weeks, the team will begin a complicated set of experiments intended to test whether IAPV can cause CCD either by itself or in combination with three other pathogens and stresses. In the meantime, Cox-Foster says, beekeepers should keep their bees as healthy as possible and not reuse hives from collapsed colonies.

If IAPV does turn out to be a cause of CCD, there is encouraging news from Israel. Sela has found that some bees can resist the virus. About a third of bees sampled in Israel have incorporated the virus into their genome. In his experiment, almost 20% of these bees survived when injected with IAPV. Sela says that raises the possibility of breeding IAPV-resistant bees.

**–ERIK STOKSTAD**

BIOMEDICINE

# HIV Drug Shows Promise as Potential Cancer Treatment

What comes around goes around: The first AIDS drug to come to market was initially developed to treat cancer, and now a drug approved for AIDS is being tested in humans as an anticancer agent.

A team led by medical oncologist Phillip Dennis at the U.S. National Cancer Institute (NCI) in Bethesda, Maryland, found evidence that drugs currently used to inhibit HIV's protease enzyme might also work against cancer. In the 1 September 2007 issue of *Clinical Cancer Research*, Dennis and colleagues describe test tube and mouse experiments indicating that three of these drugs show activity against six different types of cancer. One, nelfinavir, proved better than the others, leading Dennis to launch a clinical trial. "The amazing thing is we moved from preclinical to clinical studies in one-and-a-half years," says Dennis. Typically, pharmaceutical companies spend 5 to 10 years testing a promising compound before moving into human trials, notes Dennis, but "repositioning" an already-approved drug takes advantage of the already abundant data on toxicity and dosage.

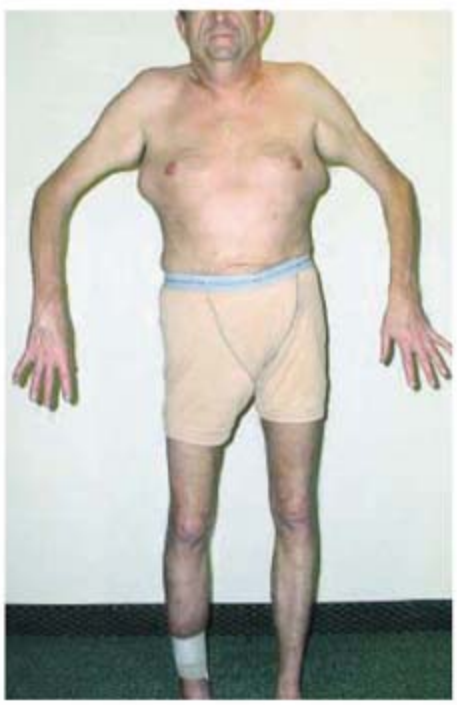
It was two toxic effects of protease inhibitors in HIV-infected people that led Dennis to the idea that they might work against many cancers. Dennis's lab specializes in studying a cell-signaling pathway, Akt, that's activated in many cancers. It's well established that inhibiting the Akt pathway can lead to a buildup of lipids and glucose. "We hypothesized that if we could identify drugs that elicited those toxicities, we would find a good Akt inhibitor," says Dennis. This led them to HIV protease inhibitors, which can cause patients to develop characteristic lipid deposits and hyperglycemia.

As Dennis and co-workers describe in *Clinical Cancer Research*, it turns out that Akt inhibition only explains part of nelfinavir's anticancer effects. "We don't think Akt inhibition is the crucial mechanism," says Dennis. Instead, they found that nelfinavir induces stress of the endoplasmic reticulum, which in turn leads cells to self-destruct through mechanisms known as autophagy and apoptosis. "The mechanism part of this paper is quite striking," says oncologist Samuel Broder, chief medical officer at Celera Genomics in Rockville, Maryland. "This is very, very interesting."

Broder, former director of NCI, in the 1980s helped discover the first anti-HIV drug to come to market, AZT, which at the time was an abandoned anticancer agent.

Dennis hopes to enroll 45 patients, all of whom have solid tumors that do not respond to treatment. Dennis initially wants to determine whether cancer patients can tolerate nelfinavir at higher doses than used to treat HIV. "The maximum tolerated dose and toxicities of nelfinavir have never been established in humans," he says. Although this could trigger the hyperlipidemia and hyperglycemia often seen in HIV-infected patients taking protease inhibitors, Dennis notes that these are controllable conditions, and, relatively speaking, not a major concern of people who have an otherwise untreatable cancer. "If we're not causing profound bone-marrow suppression and life-threatening infections, we're pretty happy," he says.

**–JON COHEN**



**Problem/solution?** AIDS drugs that caused this man's unusual fat accumulation may have revealed a new cancer agent.

CREDIT: FRANK PALELLA/NORTHWESTERN UNIVERSITY

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JAPAN

# New Centers to Have Stronger Foreign Flavor

**TOKYO**—New programs to lure foreign scientists and more funding for young researchers highlight next year's budget proposal from Japan's Ministry of Education. The 2008 request from the ministry, which funds the bulk of Japanese academic science, fleshes out the "Innovation 25" strategy announced last year by Prime Minister Shinzo Abe to grow the economy through increased spending on science and technology (*Science*, 13 April, p. 186).

Despite recent efforts, Japan's scientific institutions have attracted only limited interest from abroad and few non-Japanese researchers. But this month, the ministry expects to announce the winners of a new initiative that it hopes will address both problems. The five World Premier International Research Centers will each receive between $40 million and $170 million over the next decade in return for conducting their business in English and recruiting 30% of their research staff, and up to 20% of their principal investigators, from overseas. The ministry is seeking $80 million next year to launch the centers, which Hiroshi Ikukawa, director of strategic programs for the ministry, hopes will build reputations within their field to rival the likes of the U.K.'s Laboratory of Molecular Biology in Cambridge and MIT's Media Lab.

The government's Innovation 25 plan also aims to increase research opportunities for young scientists. Accordingly, the ministry's budget request includes a 40% increase, to $351 million, for peer-reviewed grants to those in the first decade of their career. It also contains a 45% jump in funding, to $106 million, for a clutch of programs to promote international cooperation by sending young Japanese scientists abroad, bringing foreign scientists of all levels to Japan as visiting scholars, and strengthening ties with Asia and Africa. The ministry's overall portfolio of competitively reviewed grants would grow by 22%, to $3.9 billion.

Big-ticket international projects would also benefit if the ministry's request is approved. Japan's contribution to the International Thermonuclear Experimental Reactor, under construction in Cadarache, France, would double, to $106 million. Spending on ocean drilling would increase 60%, to $159 million. And Japan's contribution to the Atacama Large Millimeter/Submillimeter Array (ALMA), a joint Japanese, European, and U.S. radio astronomy facility in the Chilean Andes, would jump 27%, to $37 million. Shoken Miyama, director general of the National Astronomical Observatory of Japan, says the additional funding will help Japan complete work on its 16 antennas in time for the scheduled start of ALMA observations in 2012.

**The road to discovery.** Japanese antennas head for the ALMA site in the Chilean Andes.

CREDIT: NATIONAL ASTRONOMICAL OBSERVATORY OF JAPAN

The 2008 request will be reviewed by the Council for Science and Technology Policy, which Miyama says "understands the value of basic research." The final hurdle, the Ministry of Finance, will likely pose a bigger challenge, says Miyama. "We don't know if the ministry will approve these requests or not."

If recent history is any guide, overall prospects are not good. Last year, the ministry initially sought a 20% increase for science and ended up with a tiny 0.4% boost, although several individual initiatives were spared. This year's requested increase for science, says Kazuo Todani, the education ministry's budget chief, would add more than 20% to this year's $20.1 billion in spending. The budget will be finalized by the end of the year and take effect on 1 April 2008. **–DENNIS NORMILE**

## An Open Secret in the U.K.

Population biologist John Beddington of Imperial College London looks likely to become the U.K. government's next chief scientific adviser when chemist David King steps down at year's end, several newspapers reported this week. An official at the Department for Innovation, Universities and Skills told *Science* that Beddington is the favored candidate in a recruitment process that remains open. An expert on the management of fisheries, Beddington currently chairs the science advisory council of the Department for Environment, Food and Rural Affairs. "He has many and varied skills and would make an excellent appointment," says ecologist Robert May of Oxford University. However, some researchers worry that a recent government restructuring by Prime Minister Gordon Brown may have diminished the science adviser's influence.

**–DANIEL CLERY**

## Just Say No

Scientists and engineers at NASA's Jet Propulsion Laboratory (JPL) in Pasadena, California, filed suit 30 August in a U.S. district court in southern California in hopes of blocking new rules that require them to submit to background checks in order to keep their jobs. The 28 plaintiffs say the checks, required by the end of September, are unconstitutional and would allow investigators to pry into their emotional state, finances, and sexual activities. "This is something straight out of the 1950's McCarthy era," says Dennis Byrnes, JPL chief engineer for flight dynamics. NASA officials say the checks, standard procedure for all government employees for decades, are simply being extended to contractors in a post–9/11 world (*Science*, 6 July, p. 31). JPL is operated by the private California Institute of Technology in Pasadena, and employees are part of the university.

**–ANDREW LAWLER**

## Sonar Ban Blocked

The U.S. Navy can continue using sonar in exercises off the southern California coast even though the noise may harm whales, a federal appeals court ruled last week. In response to an emergency motion, a panel of the 9th U.S. Circuit Court of Appeals in San Francisco voted 2–1 to stay a 6 August injunction by a district court that would have barred the sonar. "The public does indeed have a very considerable interest in preserving [whales]," the majority argued. "But it also has an interest in national defense." The court will hear the Navy's appeal of the injunction in November.

**–BENJAMIN LESTER**

PSYCHOLOGY

# Nonhuman Primates Demonstrate Humanlike Reasoning

Monkeys may see, hear, and speak no evil, but they do seem to understand a person's intentions. We constantly judge the actions of those around us, assessing what others are trying to do, and why, to decide the best course of action for ourselves. Experiments reported on page 1402 now suggest that this supposedly unique human attribute is shared by chimps and at least two monkey species. The finding suggests that this skill and the enabling neuronal circuitry date back at least 40 million years, predating the evolution of the unique social system or language of humans. It promises to fuel the debate about the cognitive divide between humans and our primate cousins.

"It's stunning evidence for [nonhuman primates'] understanding goal-directed behavior," says Melissa Gerald, a primatologist at the University of Puerto Rico in San Juan who runs a macaque research center on a nearby island, Cayo Santiago. However, she and others are not completely convinced, citing apparent flaws in the study design and analysis or concerns about anthropomorphic interpretations of the findings.

In 2002, György Gergely of the Hungarian Academy of Sciences' Institute for Psychology in Budapest shocked his fellow psychologists by asserting that 14-month-old infants could figure out what another person was trying to do and whether their behavior made sense. He assessed this ability by looking at mimicry behavior. In this experiment, an infant watched someone turn on a light with the touch of her head, not her hands. When the tester's hands were full, the infants did not mimic the head movement and instead used their hands to turn the light on. They seemed to realize that the tester had to use her head because she couldn't use her hands, although hands would work better for the task. But when the tester used her head when her hands were empty, the infants followed suit, apparently concluding that there must be a good reason to use the head in this situation. The infants not only recognized the tester's goal but also thought through the best way to achieve that goal themselves. "The infants are extremely sensitive to how efficient an action is," says Gergely.

**Test touch.** Harvard co-author David Glynn grasps a coconut shell, intentionally pointing out the shell to a macaque (not seen).

At the time, "I doubt if anyone would have put money on adult chimpanzees being able to do this, let alone monkeys," says Richard Byrne, a psychologist at the University of St. Andrews in Fife, U.K. But Justin Wood, a graduate student at Harvard University, was willing to take the bet.

Wood looked at whether cotton-top tamarins could tell a goal-directed action from a random one. In one test, he either grasped one of two food containers or flopped his hand on top of one, as if by accident, while a monkey looked on. In another, he "pointed" to the container by putting his elbow on it, sometimes while that same hand was free, and sometimes while holding an object with both hands. Wood counted how often the monkeys inspected the designated container.

This protocol was designed to evaluate whether these New World monkeys could tell a rational action (use the elbow because the hands were busy) from one that seemed less intentional. "These are very clever ways of getting at questions that are very basic to our understanding of intentionality," says Gerald.

In the first task, monkeys picked the food container Wood grasped about 75% of the time, but only about half of the time did they choose the one he flopped his hand on, indicating that the tamarins could distinguish between directed and random actions, says Wood. In the second task, they primarily paid attention to where his elbow pointed when his hands were occupied, indicating that they were attuned to what seemed to be the more rational behavior.

Wood and colleagues did similar experiments with chimps at Tchimpounga Chimpanzee Sanctuary in the Republic of the Congo (see p. 1339) and with rhesus macaques on Cayo Santiago, substituting coconuts for food containers. "We find exactly the same pattern" with the three species, says Wood.

The study raises some concerns. Gerald and others point out that the tests and number of animals used varied from species to species. For example, chimps and macaques had one chance to observe and react to a person's gestures, but tamarins were allowed a half-dozen tries. The animals could have been distracted by the free hand in the second experiment, causing them to ignore where the elbow was resting. And Daniel Povinelli and Derek Penn, who study primate cognition at the University of Louisiana, Lafayette, worry that the results may be overinterpreted. "There is, in fact, no evidence that the animals in these experiments were representing or reasoning about the [tester's] unobservable psychological states," says Penn.

This sort of reasoning is called "theory of mind," and it is usually considered to be a trait that makes humans special. "Understanding goals and efficiency is not the same as theory of mind, but it's very close to it," Gergely notes.

Close but not quite there. Some researchers contend that language is required to develop a sense of cause and effect and to evolve a theory of mind. But Wood's study indicates that such reasoning predates words, says Byrne: "It strongly suggests that this way of understanding causality is a quick-and-dirty method, not based on the kind of understanding of logic and rationality that satisfies physicists and philosophers."

–ELIZABETH PENNISI

CREDIT: JUSTIN WOOD

U.S. RESEARCH POLICY

# Med Schools Add Labs Despite Budget Crunch

The recent flattening of the National Institutes of Health budget hasn't slowed a building boom among U.S. medical schools that began during a 5-year doubling of NIH's budget in the late 1990s. That's one of several findings in a survey that offers a less gloomy picture of the health of U.S. biomedical research than many policymakers have been painting.

For the past few years, research gurus have warned that these two contradictory trends could trigger a financial crisis among universities counting on steadily rising NIH support to help meet debt payments on the new buildings and fund the research going on inside them. But the reality is not so clear-cut. According to figures released this week by the Association of American Medical Colleges (AAMC), the rise in expenditures of federal research dollars on campus has so far kept pace with the expansion of research space, despite the anemic growth in the NIH budget since 2003 (see table). Still, AAMC officials and NIH Director Elias Zerhouni worry that the trend may not continue. "It's a very anxious situation," says AAMC senior vice president David Korn.

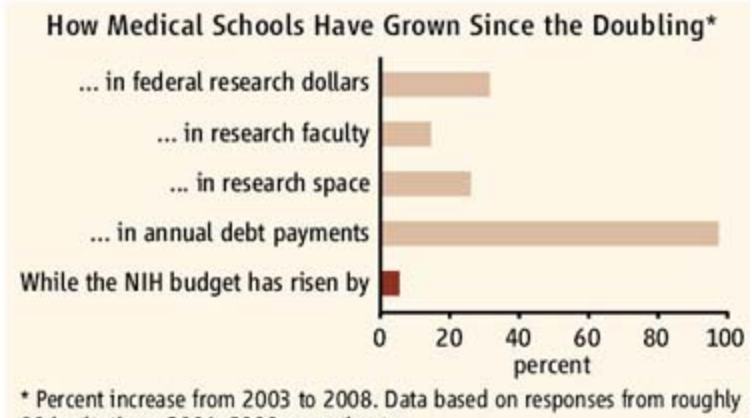
The survey updates a 2002 poll showing that member schools planned to double their spending on construction despite the looming end to the NIH budget doubling. The medical schools have followed through: The response last year from roughly 80 of 125 schools shows that institutions, on average, expect to have added 89,000 square feet of research space between 2003 and 2008. That's an increase of 26%. Accordingly, the average size of the research faculty at each institution will have risen 15% by 2008, to 381. The most striking change is a projected doubling in annual debt payments for research buildings, to $6.9 million by 2008, AAMC officials say.

At the same time, the amount of federal grant money spent by medical schools has also risen faster than NIH's budget. Federal research expenditures increased by 10.8% in 2004, for example, and by more than 5% in each of the next 2 years.

Some community leaders are troubled by those numbers. "I find myself quite alarmed at the commitment schools are making," says AAMC's Jack Krakower, who led the survey and is co-author of a commentary in the 6 September *New England Journal of Medicine* (*NEJM*) that presents the results. Zerhouni attributes the continued rise in federal dollars flowing to campuses to NIH's decision to quickly recycle money from one-time awards for new biodefense labs and other facilities into research grants. But that growth is a "temporary trend," he says. He and others say that a big crunch could come in 2008, when schools expect to have 3.7% more NIH dollars to spend.

The authors of the *NEJM* article say that the so-called crash landing is having other unfortunate consequences. Schools are chasing after a relatively small pool of well-funded researchers in "a zero-sum game" that wastes resources. Krakower also worries that schools scrambling to pay debts may rely more heavily on funding from drug companies, which usually comes with strings attached.

Those issues don't seem to trouble some rapidly growing institutions. At the University of Kansas Medical Center (KUMC) in Kansas City, vice chancellor for research Paul Terranova says the school has filled 200,000 square feet of new research space




* Percent increase from 2003 to 2008. Data based on responses from roughly 80 institutions. 2006–2008 are estimates.

CREDIT: JOHN SARTON; SOURCE: S. HEINIG *ET AL.*, *NEJM* 357, 1042 (2007)

**Mismatch.** A flat NIH budget hasn't stopped states from building new research facilities like these at the University of Arizona.

## When It's Okay to Fail

**BEIJING**—Chinese officials are hoping that a proposed change in the country's basic law governing science and technology will encourage researchers to be more honest in reporting the results of their experiments.

Last week, Wan Gang, China's new minister of science and technology, went before a working group of the National People's Congress Standing Committee to explain how the government plans to amend the 14-year-old law to promote greater innovation and creativity by fostering a "tolerance for failure" when results don't pan out. Observers say that the pressure to succeed can lead a scientist to alter results or create a culture in which peers are afraid to be critical.

But some scientists worry that the proposed revision might institutionalize mediocrity. "If failure happens, somebody ought to take responsibility and learn from it," says one legislator, physicist Chen Nanxian of Tsinghua University in Beijing. The amendment is expected to be finalized at the legislature's annual meeting in March.

**–HAO XIN**

## Laser Research Targeted

The U.S. Department of Defense plans to kill off a 20-year-old medical laser research program next month—unless Congress decides to rescue it. The Pentagon's budget request for the fiscal year that begins 1 October contained no money for the medical free electron laser program, which supports five university-based centers and researchers around the country. The $16-million-a-year competitive grants program is managed by the Air Force Office of Scientific Research, which is reviewing proposals that may never be funded.

But the program has friends in Congress. Authorizing panels in both the House and Senate strongly back continuing the research, noting its "proven track record of delivering combat casualty care technology and medical interventions." The House has approved spending $2 million for 2008, and the Senate is expected to address the issue this month when it debates the Pentagon budget. The Senate panel also asked for a strategic plan to address both the research and its applications. Supporters hope that, at the least, the program will limp along at minimal funding until the next Administration.

**–JEFFREY MERVIS**

by recruiting both established investigators and junior faculty; NIH funding has risen by 35% in the past 2 years, he notes. Terranova says that much of the expansion is being supported from private donations and that KUMC won't have to make debt payments on state bonds until 2012.

At the University of Kentucky College of Medicine in Lexington, which has hired 35 research faculty in the past 5 years, dean Jay Perman says, "We need further expansion." The school has spent $1.5 million to help investigators whose grants weren't renewed, but Perman says most applicants did better the second time around. "We're getting more new grants than we're losing grants," he boasts. University of Arizona medical school dean Keith Joiner says debt service on two new biosciences buildings, with more to come, isn't a concern because the state is covering the debt. But departments are being asked to share core resources and find other backers.

Other schools say their new labs are easing a space crunch. At the University of Wisconsin, Madison, existing faculty members quickly occupied two new research buildings. Spokesperson Terry Devitt says that the school, whose NIH funding has fallen, is more worried about "paying for the science that goes on inside" than paying for the buildings themselves.

AAMC and Zerhouni warn that the situation may get worse before it gets better. Zerhouni sees a parallel with the sudden collapse of the real estate market: Some homeowners overextended themselves, he says, with the expectation that housing prices would continue to rise indefinitely. Speaking as a former research dean at Johns Hopkins University's medical school, Zerhouni cautions, "I'd be a lot more careful [now] than I would have been in 1998." **–JOCELYN KAISER**

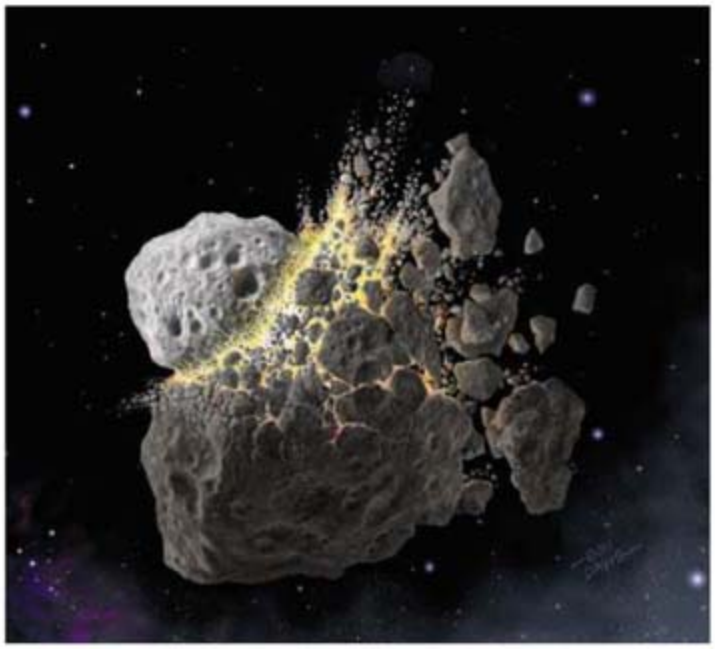
IMPACT CRATERING

# A Big Splat in the Asteroid Belt Doomed Earth's Dinosaurs

A chance encounter between two huge chunks of rock in the asteroid belt reached out across 100 million years and 200 million kilometers to snuff out 90% of Earth's marine species, as well as the dinosaurs, 65 million years ago, according to a new analysis. Nudged at first by the sun's warmth and then flung inward by Jupiter's gravity, debris from the collision eventually splattered across the inner solar system, violently cratering other asteroids, the inner planets, and the moon. The result is further evidence that "what happens in the asteroid belt leaves a trace here," says solar system dynamicist Alessandro Morbidelli of the Côte d'Azur Observatory in Nice, France. "It really makes the Earth feel like part of the solar system."

The link between earthly extinctions, the asteroid belt, and most everything in between builds on the recent discovery of hundreds of thousands of asteroids. This week in *Nature*, planetary scientists William Bottke, David Vokrouhlický, and David Nesvorný of the Southwest Research Institute (SwRI) in Boulder, Colorado, report how they used the new asteroid discoveries to identify the ancient collision's lingering debris and then calculate how and when some of that debris would have fallen to Earth.

First, the SwRI group picked out the debris fragments from an ancient collision that are scattered among myriad other asteroids in the sky. They noticed that, starting from the orbit of a 40-kilometer asteroid called Baptistina, asteroids got smaller the farther their orbits lay to either side of Baptistina's orbit. That's exactly the pattern expected of a cloud of debris eased away from the collision by the sun's rays: As each fragment absorbs solar energy, it radiates the heat away to give an ever-so-gentle rocketing effect. The members of the Baptistina "family" identified from the debris pattern also share Baptistina's color, a dark reddish hue typical of primitive meteorites that still fall on Earth. The researchers concluded that Baptistina family members formed in a single collision about 160 million years ago, judging by how far they have since drifted.



**Our own big bang.** Debris from a collision in the asteroid belt 160 million years ago may have pelted Earth and the dinosaurs.

From computer simulations of asteroid impacts, the SwRI group found that the Baptistina family could have formed in an 11,000-kilometer-per-hour, nearly head-on collision between asteroids 170 and 60 kilometers in diameter. In further calculations, the group estimated how many of the inferred 140,000 original fragments larger than 1 kilometer would have been thrown or nudged 1.4 million kilometers inward of Baptistina to a sort of orbital transfer station. There the periodic tug of Jupiter's gravity—like well-timed pushes on a child's swing—would kick some fragments into the inner solar system.

Putting it all together, the group found that the collision could explain several oddly timed impacts astronomers had noticed in the solar system. Its debris could have created the surprisingly fresh craters found on asteroid Gaspra, as well as the young rayed crater Tycho, the radiant "jewel" on the neck of the Woman in the Moon. The timing and numbers of the shower of asteroids would also explain why cratering records throughout the inner solar system hint that the impact rate has doubled during the past couple of hundred million years. And then there's the dinosaur killer. Taking into account the spectrally determined composition of Baptistina and its cousins, the SwRI group calculates that there is a better than 90% chance that the 10-kilometer object that hit Earth 65 million years ago came from the Baptistina family.

"They do a pretty convincing job," says dynamicist Derek Richardson of the University of Maryland, College Park. There's a lot of modeling, but the analysis matches what researchers see and "can explain a number of somewhat anomalous observations" with just one scenario, Richardson says. Inspired by the result, scientists gauging impact hazards are shifting their attention from high-speed but rare comets to family generating collisions in the asteroid belt. The threat from the Baptistina family may have waned, but more catastrophic disruptions are inevitable.

**–RICHARD A. KERR**

CREDIT: DON DAVIS

GENOMICS

# Venter's Genome Sheds New Light on Human Variation

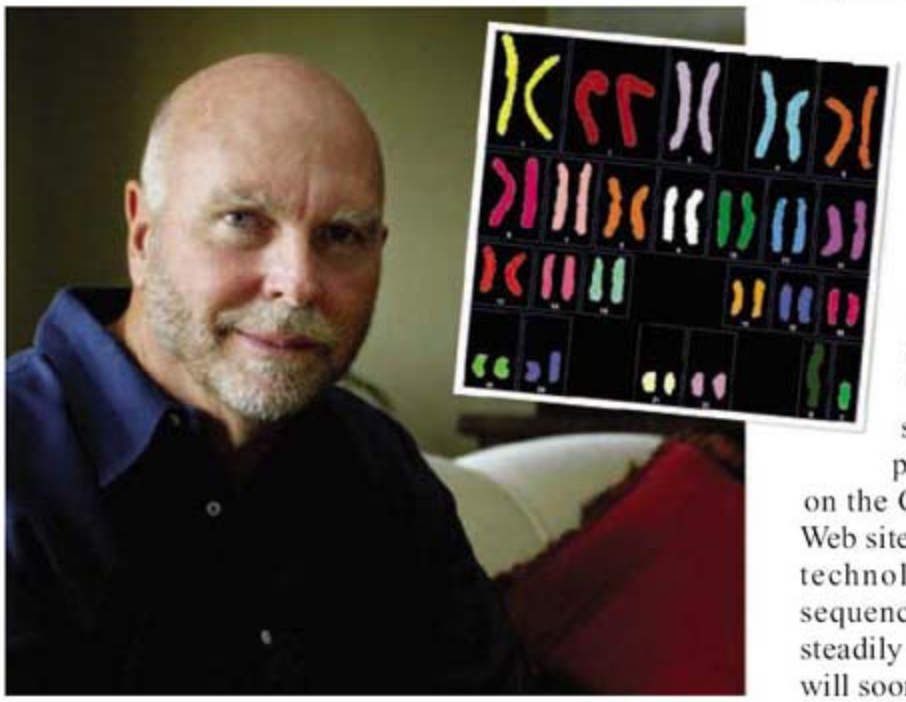
For the first time, researchers have published the DNA sequence from both sets of chromosomes from a single person: none other than pioneering genome researcher J. Craig Venter. The new sequence suggests that there is substantially more variation between humans than previously recognized. It also pushes personalized medicine a step closer and stokes long-standing debates about genetic privacy.

More than 7 years ago, Celera Genomics, a company then headed by Venter, and, separately, the international Human Genome Project consortium each described their first drafts of the genetic blueprint for a human. To save time and money, both teams combined samples from several individuals and created composite, or "reference," genomes that contained only half of a human's DNA. Humans have a diploid genome with 23 pairs of chromosomes—with one of each pair contributed by the father and the other by the mother. The reference genomes effectively have the sequence information from only one member of each pair, the so-called haploid genome. The researchers assumed that this approach wouldn't sacrifice much detail. Wrong, says a massive 31-page paper published in the October 2007 issue of *PLoS Biology* by Venter, his colleagues at the J. Craig Venter Institute in Rockville, Maryland, and collaborators from three different universities.

According to the study, haploid genomes underestimate the amount of genetic variation between individuals by a factor of 5. "We've just really underestimated this," says Venter. "We all had very naive assumptions because we didn't have that much data to go on."

Harvard University geneticist George Church, an early proponent of the Human Genome Project and a leading developer of sequencing technology, praises Venter and co-workers. "This is a great study," says Church. "We need to have diploid genomes to sort out our full inheritance. If I walk in to a doctor, it isn't going to do either of us any good if he just gets my dad's genome."

Venter and co-workers compared his two haploid genomes to assess the differences between the DNA he inherited from his mother and that from his father. Venter's DNA made up 60% of the reference genome produced by Celera; the new study built on that work, repeatedly sampling his DNA for completeness and accuracy. In all, the researchers sequenced some 20 billion DNA bases. They looked for everything from easy-to-find differences in single bases to much more obscure variations in chunks of DNA sequence that had been inserted or deleted from chromosomes.



**Vive la différence.** J. Craig Venter's genome offers the first thorough comparison of the DNA in the chromosomes inherited from each parent.

All told, the analysis found more than 4 million variants between Venter's maternal and paternal chromosomes. This suggests that humans differ by 0.5%, not 0.1%, as suggested by earlier estimates. "To understand variation, you really need to understand how much there is in the genome, and we've never really been able to do that head-on," says co-author Stephen Scherer, a medical geneticist at the University of Toronto, Canada.

Scherer hunted through Venter's genome for copy number variations (CNVs), stretches of DNA that, when compared to a reference genome, have extra or missing chunks. Scherer predicts that the rapidly growing number of investigators who study CNVs will soon begin routinely checking DNA samples against Venter's diploid genome as an additional reference. "You'd be crazy not to," says Scherer. "It's like you'd be looking at the data with one eye shut."

Some researchers, including those enthusiastic about the availability of Venter's diploid genome, question whether it actually sheds new light on the degree of variation that exists among individuals. As Harvard's Church notes, recent studies of CNVs published by Scherer and others have emphasized the same point (see p. 1315).

Venter won't be the only celebrity to have a published diploid genome for long: James Watson, co-discoverer of the structure of DNA, had his completed in May, and it's now available on the Cold Spring Harbor Laboratory's Web site. And the advent of cheaper, faster technologies such as the one used to sequence Watson's genome means that a steadily increasing number of individuals will soon join the diploid genome club.

As more individual genomes are sequenced, privacy questions will inevitably come to the fore. Watson requested that the status of a key gene that predisposes people to Alzheimer's disease not be disclosed (*Science*, 30 March, p. 1780). Venter, in contrast, went buck-naked, genetically. The paper includes a lengthy table that lists more than two dozen gene variants he has that have been associated with increased risks for alcoholism, antisocial behavior, tobacco addiction, substance abuse, heart disease, and Alzheimer's.

Venter says he has no concerns about making this information public, stressing that, in the vast majority of cases, traits and diseases are not determined by a single gene. "Will I really get Alzheimer's and heart disease?" asks Venter. His father was a smoker who died at 59 from sudden cardiac arrest, and his 84-year-old mother still plays golf and sails with him. "Who wins out?" asks Venter. "There's going to be a different answer in every one of us."

In the end, says Venter, the more people who make public their complete DNA and health histories and traits, the more readily scientists will be able to interpret the still-baffling human genome. "I don't think we have anything to fear," says Venter. "And we have a lot to gain." **–JON COHEN**

CREDITS (LEFT TO RIGHT): MATT HOUSTON/AP; J. CRAIG VENTER INSTITUTE

# Can the Wild Tiger Survive?

**China is pushing to reintroduce wild tigers, but critics say its breeding centers offer the tiger only a more roundabout path to extinction**

**HARBIN, HEILONGJIANG PROVINCE, CHINA**—For Xu Yan Chun, a wildlife geneticist at the Northeast Forestry University here, the eight Siberian, or Amur, tigers clustered in the dirt under a shade tree are a sign of hope. Although confined to a shrubby enclosure at the Heilongjiang Siberian Tiger Park in Harbin, the tigers may one day be used to help bring back what China has virtually lost: tigers in the wild. "It's the dream," says Xu, who is analyzing the genetics of the park's 800 tigers to determine how inbred they have become since the government-owned park was founded 21 years ago. He estimates that about 200 of the cats are genetically healthy enough to be used for such a captive breeding program.

Reintroducing captive tigers to the wild may seem a desperate plan. But the plight of wild tigers is indeed desperate. Just 100 years ago, an estimated 100,000 tigers representing nine subspecies roamed Asia from China to Turkey. Today, after almost unrelenting human persecution, fewer than 3000 tigers remain in the wild, according to a 2006 International Union for the Conservation of Nature and Natural Resources report. Their territory has dwindled as well, with tigers inhabiting a mere 7% of their historic range, according to leading tiger research groups. Not more than 50 wild tigers remain in China, says its State Forestry Administration (SFA).

Captive tigers, on the other hand, are booming. At least 11,000 tigers of mixed ancestry are behind bars, estimates Ron Tilson, director of conservation at the Minnesota Zoo in Apple Valley. About 1000 dwell in public zoos in Europe, Japan, North America, and other countries. Astonishingly, more than 5000 tigers are in the hands of private owners in North America. And at least another 5000 live in state and private tiger-breeding centers (or "farms," as many conservationists call them), mostly in China.

**Bone-strengthening wine?** Wine is sold in tiger-shaped bottles, but lion carcasses are used to brew it.

So in the late 1990s, when SFA officials began exploring the idea of restoring China's tigers—animals of symbolic and cultural importance to the nation—they turned in part to the tiger-breeding centers. But they are also considering other means, such as translocations of wild tigers or, if feasible, simply encouraging tiger populations to rebound on their own. "The Chinese desperately want to bring back their wild tigers," says Tilson.

But tiger reintroduction is challenging, requiring a genetically diverse population and an estimated minimum of 100 prey-packed square kilometers per tiger—not to mention the need to reacquaint captive animals with the rules of the wild. Tilson himself prefers to avoid using captive cats and is working with Chinese officials to restore the South China tiger (the most endangered of China's four subspecies) by perhaps using wild tigers of a closely related subspecies.

Indeed, for some scientists and conservationists, the captive tigers at China's five commercial breeding centers represent their worst nightmare. They argue that captive-bred tigers, often too genetically similar or hybrids, can never be released, and that unless destroyed they will be used to reignite the trade in tiger parts, which has dropped dramatically since the Chinese enacted a domestic ban in 1993. "The purpose

CREDITS (TOP TO BOTTOM): CHEN MING, SAVE CHINA'S TIGERS; IFAW (WWW.IFAW.ORG)

**Face-off.** A South China tiger prepares to attack a blesbok on a reserve in South Africa.

of the tiger farms always has been and continues to be solely for commercial purposes, to sell tiger-bone medicine and wine," charges Grace Ge Gabriel of the International Fund for Animal Welfare (IFAW), headquartered in Yarmouth Port, Massachusetts. "And if they're allowed to" sell these products, "it will mean the end of tigers in the wild everywhere."

### Tiger-bone medicine

Tigers, with their lustrous, striped furs and powerfully muscled bodies, have long been seen as embodying magical powers. For at least 1500 years, traditional medical practitioners throughout Asia have prescribed remedies using tiger bone to treat a variety of ailments from rheumatism to impotence. But in the 20th century, the tiger-bone trade increased exponentially, as did sport hunting, deforestation, and other pressures.

To stop the slaughter, in 1975 the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) banned the international trade in tigers and tiger parts. In 1993, China—often the prime destination for tigers poached elsewhere—followed this up with its own domestic ban. Yet even with China adhering to both bans, wild tigers have continued to decline in most of the 14 countries that harbor a population, largely because of shrinking habitat, lack of law enforcement, and a renewed trade in tiger skins.

The Siberian Tiger Park—China's first—was born in 1986 when a wildlife biologist decided to breed captive tigers as a source of tiger-bone medicine, with the hope of decreasing poaching pressure on the wild cats. But before any captive tiger bone parts made it to the market, China banned the trade. Struggling, this center and others turned to tourists and to selling tigers to zoos for income.

At the most recent CITES meeting in June 2007 (*Science*, 22 June, p. 1678), the centers came under fire when Ireland floated a proposal to study expanding traded items derived from captive wildlife. Several environmental organizations warned that any such expansion would be harmful to wild tigers. In response, China argued that sales from the centers could provide needed funds for conserving its few wild tigers and supporting tiger reintroduction.

Nearly every other state that has wild tiger populations and numerous environmental groups roared in protest, reiterating that such a move would doom the few remaining wild tigers by rekindling the market for tiger parts. They also called on China to close the tiger-breeding centers. "China's ban has done so much to save the tiger," says Judy Mills of the Washington, D.C.–based International Tiger Coalition. "But trade of any kind from any source and for any reason threatens its survival. Nor is there any need to reintroduce tigers. They breed like house cats and will come back on their own if they're protected from poachers."

In the end, China joined the other delegations at CITES and passed a resolution that says the captive breeding of tigers should be restricted "only to conserving wild tigers" and that the felines should not be "bred for their parts and derivatives."

Nevertheless, China has not stepped back from an internal debate about whether to allow its citizens to resume using tiger-bone medicine, although most traditional medicine practitioners argue that alternatives exist and are not requesting tiger bone. (Indeed, last May, the state-owned Tanggula Pharmaceutical Co. in Beijing published a study claiming that mole rat bones were as effective as tiger bones for treating rheumatism.) Still, some of the tiger-breeding centers sell tiger-shaped bottles containing a brew made by steeping feline carcasses in rice wine for several years, says IFAW's Gabriel. SFA officials say that the wine is made with lion bone. One center's restaurant also sold what it claimed was tiger meat as recently as last year, Gabriel adds. And the centers have hundreds of containers of tiger carcasses, skins, bones, and organs in cold storage. "They are valuable, and we hope to use them one day," says Wang Li Gang, general manager at the Siberian Tiger Park. "I'm old enough now that I myself would like to use the tiger-bone medicine."

All this creates pressure to lift China's domestic ban on the tiger-bone trade. "Since 2004, we've received many petitions ... to allow the use of tiger bone for medicines," explains Wang Weisheng, director of the Wildlife Management Division of SFA in Beijing. In 2005, SFA began researching captive-tiger breeding and the medical use of tiger bone to assess their "scientific basis," says Wang during an interview in his office. "There must be a benefit to the wild tiger from the medical use of tiger bone using captive tigers" for the ban to be lifted, he says. SFA has gathered expert input through two international tours and a workshop, he says, acknowledging that the conflict between the two positions "is very strong." He says the agency will try "to find a solution" after scientific analysis of the data.

Wang insists that the proposal is not to "reopen the tiger trade." Rather, he says, "if our government approves the use of


## Tracking the Vanishing Tiger

First listed as endangered back in 1975, the tiger (*Panthera tigris*) is disappearing faster than ever, with only an estimated 3000 surviving in the wild. Three of the nine known subspecies—Bali (*P. t. balica*), Caspian (*P. t. virgata*), and Javan (*P. t. sondaica*)—are extinct, and the South China tiger (*P. t. amoyensis*) has not been seen in the wild for 20 years. India reported a healthy population of 3642 Bengal tigers (*P. t. tigris*) as recently as 2001 but now has 1500 or fewer, according to a new, as-yet-unpublished government survey. But in Nepal and Bangladesh, Bengal tigers are holding fast, and in Russia's Far East, the critically endangered Siberian tiger (*P. t. altaica*) may be making a slight comeback. The Malayan subspecies (*P. t. jacksoni*), recently discovered via genetics, is endangered in the wild like its brethren.

SOURCE: ADAPTED FROM LUO *ET AL.*, *PLoS BIOLOGY* 2, 12 (2004)

tiger bone from captive-bred tigers, patients will only be able to buy tiger-bone medicine at designated hospitals." The regulated use of such medicines might dry up the remaining black market, he says, citing a survey by researchers at China's Science and Technology Institute in Beijing.

### Dreams of return

Even as the tiger parks push to sell tiger products, they insist that they can also help save tigers by breeding them. Indeed, the most controversial tiger reintroduction plan, called Save China's Tigers, involves using South China tigers from the Chinese Tiger Rewilding and Reintroduction Center in Meihuashan, Hunan Province—and building up stock on a reserve in South Africa, where no wild tiger has ever stalked. Started by Li Quan, a London-based businesswoman, the organization's idea is to "rewild" the captive tigers so that their offspring can survive on their own. With the approval of China's SFA, Save China's Tigers relocated two male and two female tigers in 2003 and 2004 to the South African site. They chose South Africa because "it's very hard to find enough space and prey in China," Li explains.


**Rare shot.** A wild Indochinese tiger photographed by camera trap this year in China.

Many tiger-conservation organizations remain highly critical of the plan. "It's a waste of time and money and not beneficial to the species," says Mills of the International Tiger Coalition. "It could even be dangerous, since there are questions about the genetic integrity of the captive cats," meaning that many captive tigers are hybrids of two or more subspecies. "It's better to put all our efforts into tigers that already exist in the wild."

Li says she's "been maliciously attacked for this idea by everyone, but you have to expect that with a new idea." Project manager Peter Openshaw notes that "we do not 'teach' or 'train' the tigers to hunt. … We set up situations whereby they teach themselves to hunt using their natural instincts." And it works, he says. After feeding the tigers antelope carcasses, he released three live South African antelope, or blesboks, into the male tigers' "camp." Instantly, the two tigers chased the antelope "at top speed," catching and killing first one then the other two. Most days, the tigers are fed meat; but about once a week they're allowed to hunt an antelope "to keep up their skills," says Openshaw.

The tigers will have no trouble switching prey from South African antelope to Chinese deer, predicts Gary Koehler, a carnivore biologist with Washington state's Department of Fish and Wildlife and one of Li's scientific advisers. Eventually, perhaps by next year, Li hopes the females will teach their offspring to hunt. These as-yet-unborn tigers, or perhaps the offspring of the offspring, may one day live free on a 200-square-kilometer reserve in Hunan that Li's organization and SFA plan to restore.

But other biologists worry that even if Save China's Tigers succeeds in placing a healthy, hunting tiger in that reserve, it won't be enough space, because a breeding population of 10 tigers is estimated to need at least 1000 square kilometers. SFA's Wang counters that if the reintroduction is successful, more habitat will be found. The plight of the South China tiger makes the unorthodox plan worth trying, he and other supporters insist. "If we do nothing for the South China tiger, we will lose it, so we need to be creative," says Wang.

Other reintroduction projects are under way, too, but these skirt the problem of "re-wilding" by relying on existing populations of wild tigers, even if they are from a different subspecies. For example, Tilson is working with SFA on a project to restore the South China tiger perhaps by using its close cousin, the Indochina tiger. Between 1000 and 1200 of these tigers are thought to live in scattered populations in China, Laos, Cambodia, Thailand, Vietnam, and Myanmar. "Morphologically and genetically, you really can't tell them apart," says Tilson, adding that the subspecies differences are "biopolitical differences. The historical designations are there only because there is a border." The tigers would be given a 1000-square-kilometer preserve straddling Hunan and Hubei provinces.

Tilson's proposal with SFA calls for converting the existing pine and fir trees ("You can't really call it a forest, since the trees are planted like rows of corn, and there's not a weed or bird or mammal in sight," he says) to the original habitat of shrubby grassland, then building up populations of native deer and boar, the tiger's preferred entrées. Once habitat and prey are restored, and villagers (Han Chinese intellectuals who fled here during the Cultural Revolution) relocated, Indochina tigers would be brought in from another as-yet-unidentified population, probably young tigers leaving their mother's territory. "They will do just fine," Tilson predicts. He hopes that the project will eventually "give China and other countries a model that can be used elsewhere."

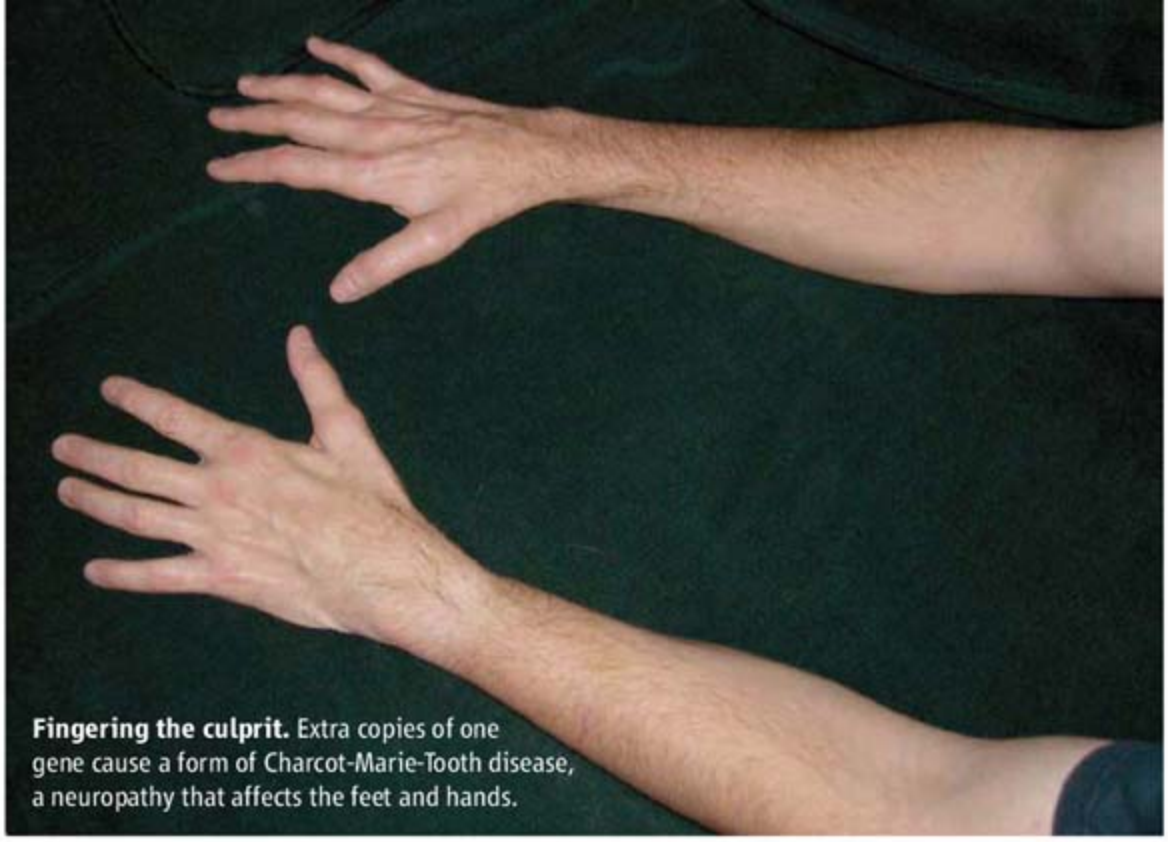
Meanwhile, in Yunnan Province near Laos, James L. David Smith, a wildlife biologist from the University of Minnesota, St. Paul, and Zhang Li, a wildlife biologist at Beijing's Normal University, are working to bring back the Indochina tiger itself; no more than 16 are thought to live in China. Still, "there are three reserves that potentially have populations," says Smith, who with Zhang and Yunnan's forestry department has launched an in-depth survey. In April, one of Zhang's students photographed an Indochina tiger inside one of the reserves (see photo, left). If the team finds a breeding population in China, Smith suggests that the Chinese follow his plan for Nepal, where he encouraged the government to work with local communities to protect the tiger. "There are now more tigers in Nepal [about 120] than when I did my Ph.D. research in the 1970s and '80s," he says, largely because of increased mixed forest cover. "That is the key: good tiger habitat."

Back in Beijing, Wang hasn't given up on captive tigers. If the Save China's Tigers project succeeds, he says he might consider a reintroduction program for the Siberian tiger, too, using some of the genetically healthy captive Siberian tigers Xu has identified at the Siberian tiger-breeding center. But that remains only an idea. For now, these Siberian tigers will remain in captivity, entertaining tourists on the Number One Adventure Bus, chasing chunks of raw meat, mating with their close relatives, living, as most tigers do these days, behind bars; their fate after death uncertain.

**–VIRGINIA MORELL**

Virginia Morell is a science writer in Ashland, Oregon.

CREDIT: BEIJING NORMAL UNIVERSITY/XISHUANGBANNA NATIONAL NATURE RESERVE



**Fingering the culprit.** Extra copies of one gene cause a form of Charcot-Marie-Tooth disease, a neuropathy that affects the feet and hands.

CREDIT: CHARCOT-MARIE-TOOTH ASSOCIATION; SOURCE: LEE *ET AL.*, *NEURON* 52, 103–121 (2006)

GENOMICS

# DNA Duplications and Deletions Help Determine Health

**Each human's genome is distinguished by extra, and sometimes missing, DNA that can powerfully impact everything from development to disease**

In 1991, both *Science* and *Nature* turned down James Lupski's submission that described an unprecedented link between an inherited human disease and a novel chromosome aberration. "It was rejected without even being sent out for review," recalls Lupski, a geneticist at Baylor College of Medicine in Houston, Texas. Unlike the many studies that fingered tiny mutations in genes as the cause of inherited diseases, Lupski pointed to a relatively large, duplicated region of one chromosome as the culprit. Later research showed that this duplication, inserted within the same chromosome, harbors an additional copy of a gene involved in making a nerve cell's protective sheath. The extra dose of the gene caused the sheaths to disintegrate, interrupting signals between the brain and the hands and feet. At the time, "there was no appreciation that copy number was a mechanism of disease," says Lupski, whose study appeared in *Cell* later that year.

Lupski's link between gene copy number and the peripheral neuropathy known as Charcot-Marie-Tooth disease (CMT) marked the opening of a new chapter in human genetics. Not only has his discovery led to progress in understanding and potentially treating this devastating disease, but it also set the stage for what has recently become a frenzy to find other connections between disease and gene duplications or deletions. As new techniques to spot such genetic differences have become available, investigations of the human genome have found thousands of variations in the number of copies of a gene, a piece of a gene, or large stretches of DNA—so-called copy number variants, or CNVs. "This whole new world has been opened up in genetic variation," says cytogeneticist Charles Lee of Brigham and Women's Hospital in Boston.

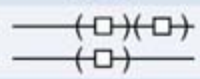
Geneticists are steadily linking more and more of these CNVs to human maladies, including Alzheimer's, Parkinson's, various mental retardations, autism, color blindness, and anatomical deformities. Several studies have shown that CNVs can also powerfully influence a person's susceptibility to disease and to the side effects of medications. And each connection between a CNV and a disease suggests novel targets for therapies.

CNVs have become such hot commodities that some researchers now contend they're as important as mutations in genes themselves. And several companies that specialize in analyzing DNA have developed new tests to detect CNVs. "We're starting to see CNVs incorporated into most genetic studies now," says Stephen Scherer, a medical geneticist at The Hospital for Sick Children in Toronto, Canada.

But with all the excitement surrounding CNVs, several leading researchers in the field urge colleagues to keep their enthusiasm in check. One caveat is that the main technologies used to pick out duplications and deletions are relatively blunt tools, leading to widespread concern that far more CNVs have been reported than truly exist. "There's a lot of hype in the CNV field right now," says Lee.

Yet there's growing agreement that CNVs can have a profound influence on determining what makes individuals unique, reaching far beyond health status to affecting underlying differences in looks and personalities. "What's cool is that we're a mosaic of pieces of genomes," says Evan Eichler, who studies gene duplications at the University of Washington, Seattle. "None of us is truly normal."

## Gene Dosage Affects Symptoms

| | GENE COPIES | PHENOTYPE |
|---|---|---|
|  | 2 | Normal |
|  | 3 | CMT1A |
|  | 1 | HNPP |
|  | 4 | Severe CMT1A |
|  | 3 | Mild CMT1A HNPP features |

**Numerous possibilities.** The number of extra, missing, and mutated (red) *PMP22* genes leads to neuropathies (CMT1A and HNPP) of varying severity.

## Beyond belief

Geneticists have long known that extra or missing chromosomes or chromosome fragments, visible under a microscope when a cell's DNA is stained, can cause conditions such as Down syndrome. They have also tied scores of diseases to molecular misspellings: mutations in individual bases that make up the DNA in a gene. But, as Lupski discovered, other things can go haywire in the human genome. Pieces of chromosomes too small to see with a microscope can break off, attach in the wrong place, or duplicate, creating "structural variations" that range in size from 2 to 2 million bases. A piece of a gene, a whole gene, or many genes can get caught up in these rearrangements, which occur as DNA is copied during cell division.

Until recently, these submicroscopic changes have escaped routine detection. Indeed, until the human genome was sequenced, researchers had few clues about their existence. Now, with a reference sequence in hand and new techniques to analyze DNA, discovery of structural genetic differences in an individual has become commonplace, and there's an increasing appreciation of how big a role they play in making each

person's genome distinct. "The field is moving very fast," says Lupski.

The identification of these variations has upped the ante on the subtle ways humans differ. Over the past decade, studies that compare DNA differences between individuals have found that single base changes, called single-nucleotide polymorphisms, or SNPs (pronounced "snips"), are abundant, occurring as frequently as once every 100 bases in the 3-billion-base-long human genome. Now CNVs—which by definition are DNA stretches of 500 bases or more that differ from the human genome reference sequence—are proving to be more common than previously thought.

In 2004, two reports that detailed the frequency of CNVs stretched many minds. First came a paper in the 23 July 2004 issue of *Science* (p. 525) in which Jonathan Sebat and Michael Wigler of Cold Spring Harbor Laboratory in New York state and colleagues described the results of their search for CNVs in 20 "normal" individuals. They found 211 CNVs. That was far more than they and others expected, but welcome confirmation came a week later when *Nature Genetics* published a paper online from the labs of Toronto's Scherer and Brigham and Women's Lee, who analyzed 39 healthy people and found 255 CNVs. In both studies, the average person had about a dozen CNVs. When they first submitted their paper, says Scherer, the total known human CNVs, including the one Lupski had found, numbered just 12. "Two of three reviewers said, 'This just can't be true. We would have seen it before,'" Scherer recalls.

Scherer, Lee, and other colleagues have since created a Database of Genomic Variants to catalog all reported CNVs in normal humans. As of their most recent update in March, they had compiled 6482 CNVs from 40 publications. Just this week, in the 4 September issue of *PloS Biology*, researchers describing J. Craig Venter's genome sequence reported that this sequencing maverick has more than 60 CNVs, half of them losses and half of them gains (see News story by Cohen).

## Start making sense

Discovering a variation in gene copy number is now the easy part, says geneticist Matthew Hurles of the Wellcome Trust Sanger Institute in Hinxton, U.K. "The much harder thing is to determine its impact." Toward that goal, Hurles and colleagues have put together DECIPHER, a database that catalogs CNVs linked to disease. And as part of the Genome Structural Variation Consortium, Hurles, Scherer, and Lee are searching for additional functionally relevant CNVs. In the 23 November 2006 issue of *Nature*, the consortium reported analyzing 270 healthy individuals from four distinct ethnic populations. They found that 14.5% of the CNVs in these people included genes already identified as having a role in inherited disorders, suggesting that the variants may be key in a wide variety of afflictions.

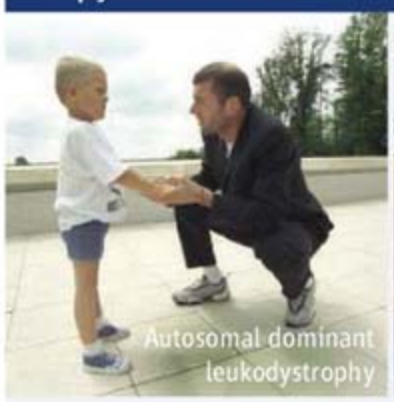
The consortium looked at individuals from the same populations to determine the relative importance of CNVs and SNPs in altering gene expression. In the 9 February issue of *Science* (p. 848), the researchers reported that CNVs accounted for 17.7% of gene-expression differences, whereas SNPs accounted for the rest. These findings, they concluded, underscore that significant genetic variation can involve everything from a single base change to millions of bases.

Yet finding that a CNV alters gene expression or involves a disease-related gene is still a far cry from explaining how it actually causes symptoms. As it turns out, CNVs can cause problems by several different mechanisms. In the simplest scenario, extra or missing copies of a gene alter its overall expression, thus changing production levels of the protein encoded by the gene.

Genes typically come in pairs, one in each set of chromosomes. A single missing gene can reduce protein production, and if both copies are missing, it can shut down production altogether. Such missing genes cause everything from neurodevelopmental disorders (including the syndromes known as Williams-Beuren, Smith-Magenis, Prader-Willi, Angelman, and Miller-Dieker) to color blindness and predisposition to Crohn's, lupus, and AIDS.

Gene duplications—which can range from one to more than a dozen copies of a gene—in contrast, can increase protein production. As Lupski discovered, such excess leads to a form of CMT. Studies of families with early-onset Alzheimer's disease have found that extra

## Copy Number Variants Involved in Human Disease






| DISEASE | GENE | PHENOTYPE |
|---|---|---|
| Charcot-Marie-Tooth type 1A | *PMP22* | Demyelination, peripheral neuropathy |
| X-linked hypopituitarism | *SOX3* | In males, short stature, mild mental retardation |
| Autosomal dominant leukodystrophy | *LMNB1* | Demyelination, white brain matter abnormalities |
| Parkinson's | *SNCA* | Neuron degeneration, rigidity, tremor |
| Alzheimer's | *APP* | Amyloid β precursor protein buildup |
| Altered drug metabolism | *CYP2D6* | Increased side effects, increased or decreased efficacy |
| HIV/AIDS | *CCL3L1* | Increased susceptibility to infection and disease |
| Lupus | *FCGR3B* | Increased susceptibility to kidney failure |
| Smith-Magenis syndrome | *RAI1* | Mental retardation |
| Pelizaeus-Merzbacher | *PLP1* | Demyelination, paralysis of legs, involuntary jerking of head |
| Spinal muscular atrophy | *SMN1* | Spinal deterioration, milder disease w/later onset |
| Rett-like syndrome | *MECP2* | Mental retardation, spasticity, language/speech problems |
| Miller-Dieker syndrome | *LIS1* | Brain malformation, mental retardation, epilepsy |
| Neurofibromatosis type 1 | *NF1* | Tumors, cognitive deficits |

CREDITS (TOP TO BOTTOM): CORBIS; AP; ALIX/PHOTO RESEARCHERS; SOURCE: LEE AND J. LUPSKI/BAYLOR COLLEGE OF MEDICINE; CONRAD AND ANTONARAKIS/UNIVERSITY OF GENEVA MEDICAL SCHOOL

copies of genes can overproduce the amyloid β precursor protein, causing problems for the brain. Similarly, geneticists studying a rare form of early-onset Parkinson's have found that it can result from a CNV that causes the overproduction within the brain of the protein α-synuclein.

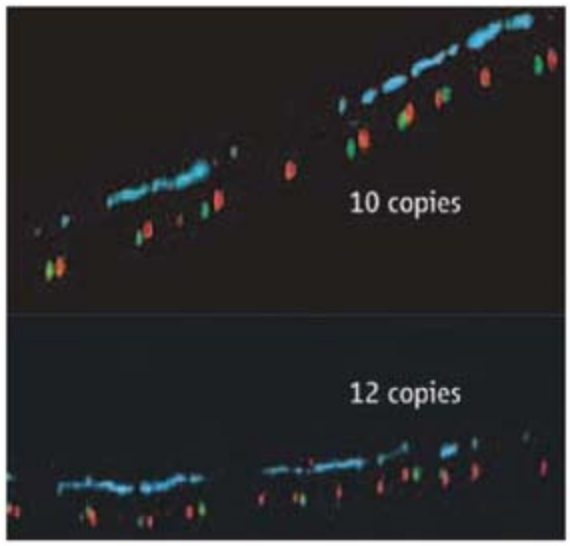
But unraveling the ties between CNVs and disease isn't always straightforward. Having an extra or missing gene often has no appreciable impact. Sometimes an extra copy of a gene includes a SNP, making it different from the normal copies, and it's that single-base mutation that causes problems. The SNP, in turn, might modify the effect of the CNV, lessening or exacerbating the resulting symptoms. Other times, the CNV alters the regulatory mechanism that controls a gene located far away. Or the creation of a CNV can add or delete DNA in the middle of an existing gene, effectively crippling it.

"It's a whole different thing to go from finding a CNV to determining which are the dosage-sensitive genes" relevant to a disorder, says Lupski. He notes that it took his group several years after linking a CNV to CMT to demonstrate that it was extra copies of the gene *PMP22* that led to disease by increasing production of its protein.

Given the difficulty of proving causation, there's a growing concern that some researchers have been too quick to pronounce disease associations with duplications and deletions. "It seems right now that there's this fervor with CNVs, and everyone's testing their disease cohort and saying, 'We found a connection that's never been seen,' " says Eichler. One much-discussed example of a result that hasn't held up: a report in the 10 August 2001 issue of *Cell* that tied susceptibility to phobia and panic disorders to a duplicated region of chromosome 15. Five subsequent studies found no such association.

Eichler and other researchers worry, too, that the literature—and thus the Database of Genomic Variants—is littered with too many large CNVs, which typically stretch for several thousand bases. Eichler notes that all of the bases encompassed by the 6500 CNVs in the database added together account for more than 20% of the genome, a notion he brands as "absolutely bogus." Says Eichler, "They're overinflating the real estate." Scherer, on the other hand, suspects that the literature currently underestimates the true number of CNVs.

Some of this debate stems from limitations of the technique most commonly used to detect CNVs, comparative genome hybridization. Adapted from cancer research, the technique takes advantage of the fact that a single strand of DNA will stick, or hybridize, to its complementary strand. So researchers use a known strand of DNA as a target, and then compare how much of an unidentified strand hybridizes in comparison to the amount of hybridization seen with the known complementary strand. Powerful as the technique is, it sometimes detects DNA differences that do not exist or reports the same CNVs as unique. Ideally, researchers would compare a person's actual DNA sequence to the reference genome. Although this is a much more expensive process, Eichler and colleagues plan to employ this sequence-level strategy to gather details about the deletions and duplications in more than 50 individuals, thereby getting a handle on the true numbers of CNVs.




**Red alert.** Two chromosomes contain different copy numbers (red dots) of a gene that codes an amylase, an enzyme that breaks down starch.

CREDIT: CHARLES LEE, BRIGHAM AND WOMEN'S HOSPITAL

### Into practice

Once a CNV is conclusively linked to a disease, how does that help people? "That's a burning question for the whole field and for SNP associations as well: How do you translate that information into a pharmacological strategy?" says Steve McCarroll, a geneticist who works on both CNVs and SNPs at the Broad Institute in Cambridge, Massachusetts.

Researchers have made tangible headway with CMT type 1A disease, about 70% of which is caused by an extra copy of *PMP22*. In the April 2004 issue of *Nature Medicine*, a team led by Michel Fontés of the French biomedical research agency INSERM in Marseille, France, described engineering mice to overexpress the human *PMP22* gene, mimicking the CNV Lupski had found in people. The researchers demonstrated that high doses of vitamin C reduced the expression of *PMP22* in the mice, which led to remyelination of their damaged axons and improvements in their locomotion. In April, researchers at Wayne State University in Detroit, Michigan, began studies with high doses of vitamin C in patients with the CMT type 1A duplication. Results are expected in 2010. "It's all very, very early," says Lupski.

Pharmacogenomics researchers, who examine how genetic variations affect individual responses to drugs, are finding it useful to consider CNVs as they evaluate new treatments and unravel why some people don't respond to existing medicines. They now know, for example, that in the subset of cancer patients who have extra copies of the *PMP22* gene, the chemotherapeutic vincristine accelerates the neuropathies seen in CMT type 1A and should not be used. Another potential application of CNV identification to personalized medicine involves *CYP2D6*, a gene that codes for a liver enzyme and partially controls how people metabolize drugs.

And researchers last year discovered that variations in the number of copies of a gene involved with steroid metabolism, *UGT2B17*, might explain variations in testosterone levels in athletes. In a study, *UGT2B17* was deleted more frequently in Korean than in Swedish men, leading to higher testosterone levels in the Swedes. Such work could improve drug-doping testing of competitors by distinguishing people who take artificial testosterone from those with normally high levels in their body.

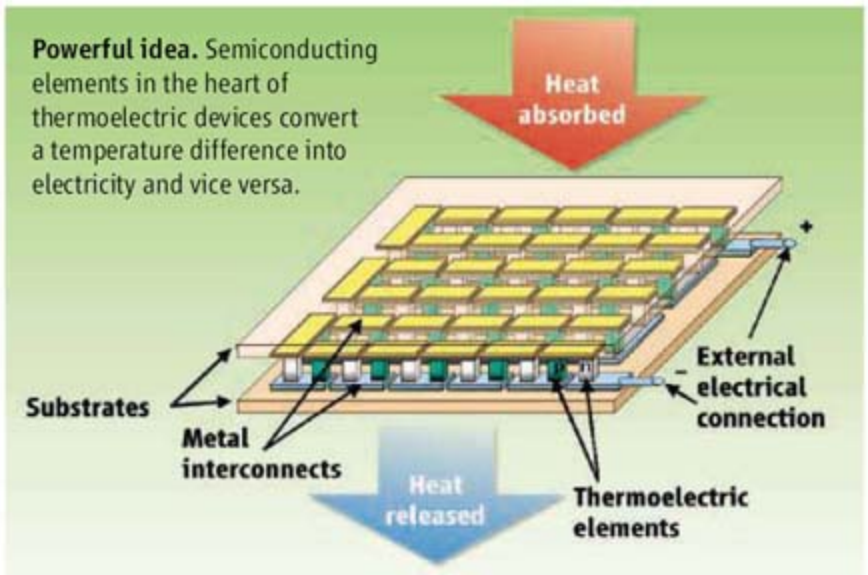
Figuring out the true role CNVs ultimately play will depend heavily on the accuracy of the technologies used to detect them and the populations that researchers tap to assess links to disease. Many genomics companies recently have put serious muscle into developing better assays and have begun to collaborate with groups that have collected DNA from well-characterized populations. Iceland's deCODE Genetics, which has made great strides identifying associations between SNPs and disease in its large database of more than 100,000 Icelanders, has teamed up with assaymaker Illumina in San Diego, California. "We have a very significant effort looking for CNVs," says deCODE CEO Kári Stefánsson. McCarroll and David Altshuler at the Broad Institute have joined forces with Affymetrix in Santa Clara, California, to develop assays that simultaneously detect both SNPs and CNVs. And NimbleGen Systems in Madison, Wisconsin, announced in July that the Genome Structural Variation Consortium will use the company's new comparative genome hybridization assay, which can map CNVs that are as few as 500 bases long—100 times finer resolution than the group used in the map it published last year.

Lupski, who has watched the field grow from its inception, says to expect many more surprises. "We're charting new territory, and we don't know where we're going to sail to," he says. "And that's fun." **–JON COHEN**

# Silicon Adds to Its Roster of Skills

Is there anything silicon can't do? The silvery semiconductor is already the behemoth of the electronics world. Researchers have engineered it to manipulate light as well. Now, a California-based team has found that collections of whiskerlike silicon nanowires make an impressive thermoelectric material, capable of converting heat flow into electricity and vice versa.

At the meeting last month, James Heath, a chemist at the California Institute of Technology (Caltech) in Pasadena, reported that by simply growing silicon into wires about 10 nanometers across, he and his colleagues improved silicon's ZT—a measure of how well a material converts heat flow to electricity—to 1, roughly 100 times that of bulk silicon. "It's a really important finding," says chemical engineer Gyeong Hwang of the University of Texas, Austin. Although a ZT of 1 lags behind the record of 2.4, silicon is a far simpler material than the current record holder—a complex, multilayered material. That advantage, together with the computer industry's decades of experience working with silicon, means that silicon-based thermoelectric devices could one day be incorporated into computer chips to help cool them down and may eventually help turn waste heat from boilers and car engines into valuable electrical power.




**Powerful idea.** Semiconducting elements in the heart of thermoelectric devices convert a temperature difference into electricity and vice versa.

The thermoelectric effect, discovered nearly 200 years ago, works when a semiconductor is hotter on one side than the other. Heat and electrical charges flow from the warm side to the cool one. The movement of charges creates a voltage difference between the two sides that can be harnessed to do work. The effect also works in reverse: Apply a voltage, and the semiconductor pushes heat from one side to the other. So far, thermoelectric devices have been too inefficient to compete with other power-generating or heat-pumping technologies. But experts think large-scale markets could open up if a thermoelectric device achieved a ZT of about 3, or perhaps less if the starting material were cheap.

The key to making efficient thermoelectric devices is finding materials that are good electrical conductors but prevent heat-carrying vibrations, known as phonons, from traveling across the material's crystal lattice. Phonons equalize the temperature on both sides and so eliminate the material's ability to generate power. Thermoelectric devices made from alloys of bismuth and tellurium with a ZT of about 1 have been around for decades. But in the mid-1990s, physicists in Massachusetts and Pennsylvania calculated that the effect would spike if the semiconductor were just a few nanometers thick in at least one dimension. Such a shape would allow electrons to continue to whiz through the materials but would block phonons from carrying heat from one side of the device to the other. In 2001, researchers in North Carolina hit the jackpot with devices showing a ZT of 2.4, made from a complex sandwich of semiconductor layers, each as little as 1 nanometer thick.

Heath and colleagues decided to see what would happen if bismuth had two nanometer-scale dimensions instead of one—nanowires instead of sheets. Heath's team had previously developed a technique for making perfect nanowires from many different kinds of materials (*Science*, 4 April 2003, p. 112) and applied it to forge bismuth nanowires. But chemical reactions on the surface of the wires interfered with thermoelectric measurements. The Caltech team decided to try nanowires made from silicon instead. Silicon has dismal thermoelectric properties in bulk, but because its surface can be carefully controlled it seemed an ideal test bed. The tests showed a pleasant surprise: The electrical conductivity of the nanowires dipped slightly compared to the bulk, but the thermal conductivity went through the floor, dropping 1000-fold.

Heath suspects the drop is due to "phonon drag," in which phonons slow their movements because of interactions with electrons. If so, he adds, it suggests that the material's small dimensions, rather than its surface chemistry, is responsible. In any case, Heath says he suspects that spiking silicon with other elements to improve its electrical conductivity and slow phonons even further may give silicon nanowire thermoelectric devices yet another boost—possibly enough to hand silicon yet another job in the electronics world.

# Antisense Particles Send Up a Flare

It takes skill and a bit of luck to succeed in science. So far, antisense technology, which tries to shut off the output of particular genes, has shown plenty of the former but little of the latter. The technique has long excelled in lab studies, but antisense-based drugs have struggled to reach the market. In many cases, researchers have been left wishing they could see what went wrong. Now they may be able to.

At the ACS meeting, chemist Chad Mirkin of Northwestern University in Evanston, Illinois, reported that his team has managed to create tiny particles that not only turn off the activity of genes inside cells but also send off cellular signal flares when they do, allowing researchers to instantly see whether their gene blockers are working or not. "It was a nice talk," says Zeev Rosenzweig, a chemist at the University of New Orleans in Louisiana. Although the technique isn't the only one that can be used to gauge patterns of gene expression, early indications suggest it well outperforms the competition.

Antisense technology works by interfering with the cellular assembly line that first converts DNA into RNA, and then RNA to proteins. The process can be inter-

CREDIT: JAMES LIM AND JEFF SNYDER/JPL/CIT

rupted at different steps, but the method used most frequently is to introduce into cells DNA strands complementary to those transcribed from the gene. When those complementary strands encounter one of their closely related messenger RNA (mRNA) brethren, they bind to it and both are removed from the assembly line.

Numerous techniques have been offered over the years for getting antisense DNA and RNA strands inside cells, including placing them inside viruses or tiny plastic capsules, or directly injecting them. But each has produced its own problems. Polymers, for example, are only modestly effective at getting a plentiful number of strands inside the cell. Even if you can get antisense strands into the cells, it can be difficult to know just how much of it is binding to and interrupting its targets. One scheme for judging success is to add small loops of DNA with inactive fluorescent molecules attached. When the DNAs bind to their target mRNAs, they unfurl, which activates the fluorescence. But these DNA loops don't survive long in cells because they are quickly chewed up by enzymes, and introducing them into the cell requires carriers that can have toxic side effects.

Last year, Mirkin's group began working on a new antisense technique. In the 19 May 2006 issue of *Science* (p. 1027), they reported that they were able to coat gold particles 13 nanometers across with dozens of identical DNA snippets. A wide variety of cultured cells seemed happy to take up the particles, and the researchers showed that RNAs in the cell would bind to the DNA-studded particles and strongly lower protein production.

For their current work, Mirkin's group improved these particles by creating nanoflares that report their success in sopping up RNA. The researchers start by creating strands of DNA that are 18 bases long and attaching these to their tiny gold particles. They then create complementary strands 10 bases long that also have a fluorescent label attached and allow the two to mate up. That leaves their gold nanoparticles with dozens of these double-stranded complexes, an arrangement that inactivates the fluorescent labels.

Next, the researchers introduce the DNA-studded particles into the cell. If complementary mRNAs are present, they bind to the long DNA strand, because their ability to bind all 18 nucleotides allows them to displace the short DNAs. The ousted short strands then drift away, which activates the fluorescent label and sends off a tiny flare. At the meeting, Mirkin reported that his team used the technique to track the downturn in expression of a cancer-promoting gene in a cancer cell line known as SKBr3.

Mirkin and others say it's still too early to know whether this nanoparticle-plus–signal flare system has a therapeutic future. But the material didn't show any toxicity in early in vitro studies. And even if the new complexes are never used as drugs, biologists still have a new multitalented probe that can ferry DNA into cells, light up mRNA binding, and regulate gene expression all by itself.

**–ROBERT F. SERVICE**

## DIPSTICK TEST FLAGS SPOILING FOOD

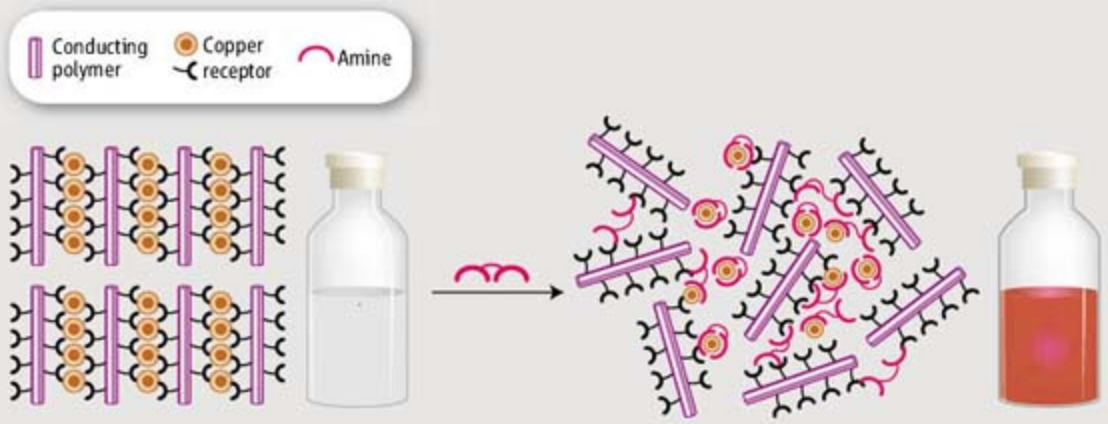
If you've ever wondered whether that piece of fish you bought at the market has started to go bad, help may soon be on the way. At the ACS meeting, John Lavigne, a chemist at the University of South Carolina, Columbia, reported that he and colleagues have developed a dipstick-style sensor that changes color at the early stages of food spoilage in fish. "It's an interesting approach," says Sean O'Keefe, a food science chemist at Virginia Polytechnic Institute and State University in Blacksburg. "Any type of tool like this that can be inexpensive and made in large quantities is of great interest to the seafood industry."

Food scientists of all stripes are interested in coming up with such devices in the hope of reducing the 75 million cases of food poisoning each year in the United States alone. Different foods generate different chemical profiles as they begin to spoil. In tuna and many other fish, bacteria that begin to break down the meat chop carboxylic acid groups off amino acids, generating a wide range of compounds called biogenic amines. Researchers have shown how biogenic amines, such as histamine and cadaverine, increase as food begins to spoil. But the analytical equipment for carrying out such tests costs tens of thousands of dollars, well beyond the reach of your average consumer.

Lavigne and his colleagues suspected they could do it more cheaply with the help of polymers that conduct electricity. There's increasing interest in conducting polymers as sensors because the polymers can change their conductivity and even their color as the orientation of the polymers change. So Lavigne's team started by adding carboxylic acid groups to conducting polymers to allow them to bind to a wide range of amines. When amines bind to these carboxylic acids, it prompts a shape change and a corresponding change in color as well.

But the color change still was less than the group would have liked. So the researchers added copper to the solution containing the polymer. The copper causes links to form between many of the polymer chains. As a result, the polymers precipitate out of solution, leaving it clear. When the researchers then added amines, those broke some of the cross-links with the copper and forged bonds with the carboxylic acids, allowing the polymers to dissolve back into the solution. The upshot was that the researchers saw a much sharper set of color changes from red to purple depending on the amount and types of amines added. Adding metals other than copper up front also gave them different color changes, which they could use in combination to fingerprint specific amines being generated.

Finally, the researchers incorporated their conducting polymer material into a dipstick sensor, similar to those used in home pregnancy tests, and showed it was able to gauge the degree of spoilage in various fish samples. Lavigne says he has already begun discussions with a Michigan-based company to make cheap sensors that consumers can use to ensure the food they are about to eat is safe. **–R.F.S.**




**Spotting trouble.** Copper atoms cause conducting polymers to clump and fall out of solution (left), while adding the amine target molecules breaks the pack and causes the solution to change color (right).

CREDIT: P. HUEY/SCIENCE; SOURCE: ADAPTED FROM JOHN LAVIGNE/U. OF SOUTH CAROLINA, COLUMBIA

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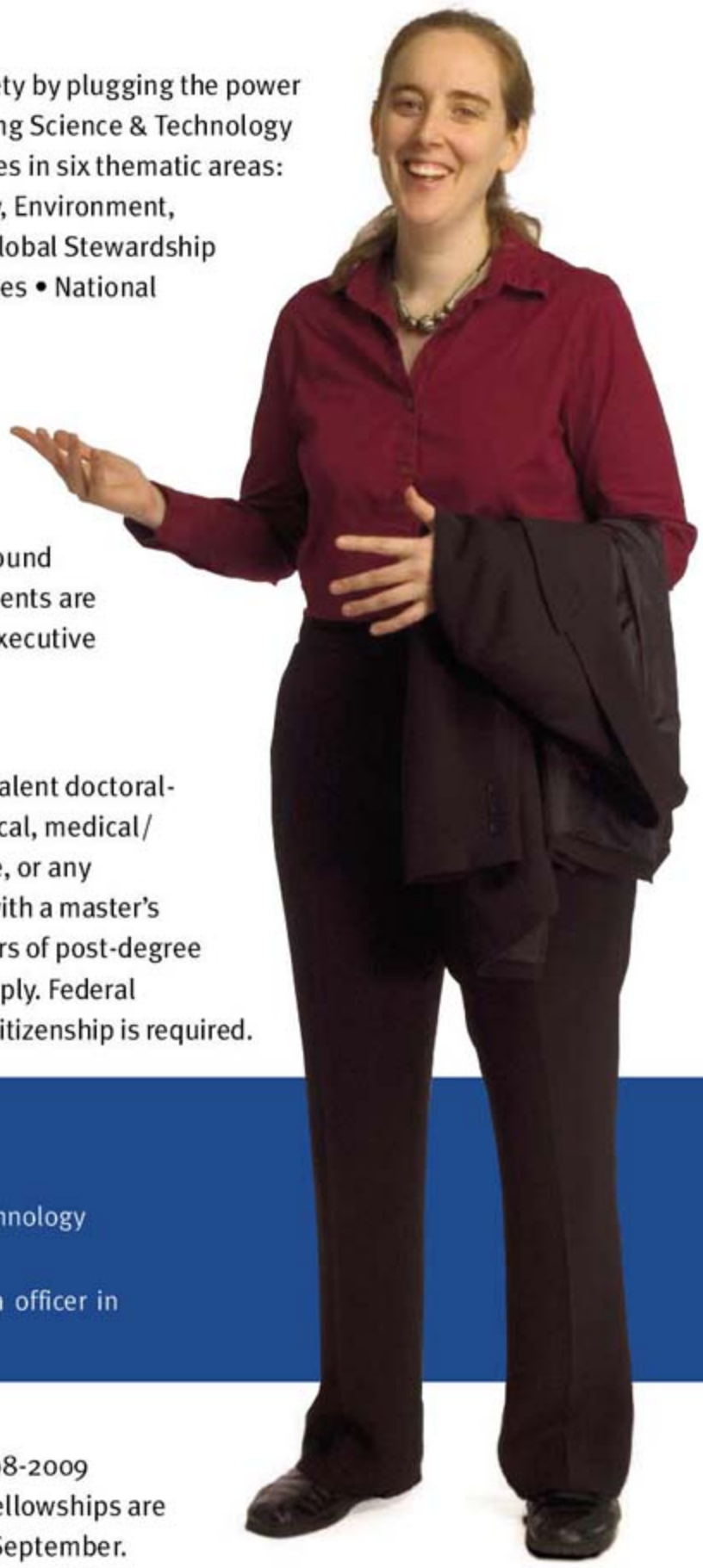

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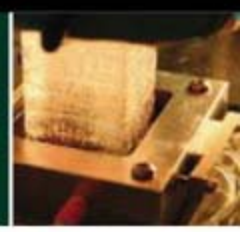




# LETTERS

*edited by Etta Kavanagh*

## A Proposal for a Decade of the Mind Initiative

A DEEP SCIENTIFIC UNDERSTANDING OF HOW THE MIND PERCEIVES, thinks, and acts is within our grasp. Such an understanding will have a revolutionary impact on national interests in science, medicine, economic growth, security, and well-being. It is our belief that paradigm-shifting progress can be made now by establishing a major national research initiative called "The Decade of the Mind."

A Decade of the Mind initiative would build on progress of the recent Decade of the Brain (1990–99), which dramatically increased the visibility of neuroscience (*1*). Unlike the Decade of the Brain, which focused on neuroscience and clinical applications, the Decade of the Mind initiative, by necessity, should be transdisciplinary and multi-agency in its approach. Success will require research that reaches across disparate fields such as cognitive science, medicine, neuroscience, psychology, mathematics, engineering, and computer science. Additional important insights will need to come from areas as diverse as systems biology, cultural anthropology, social science, robotics, and automation technology.

For these reasons, we believe a Decade of the Mind initiative should focus on four broad, but intertwined areas (see figure).

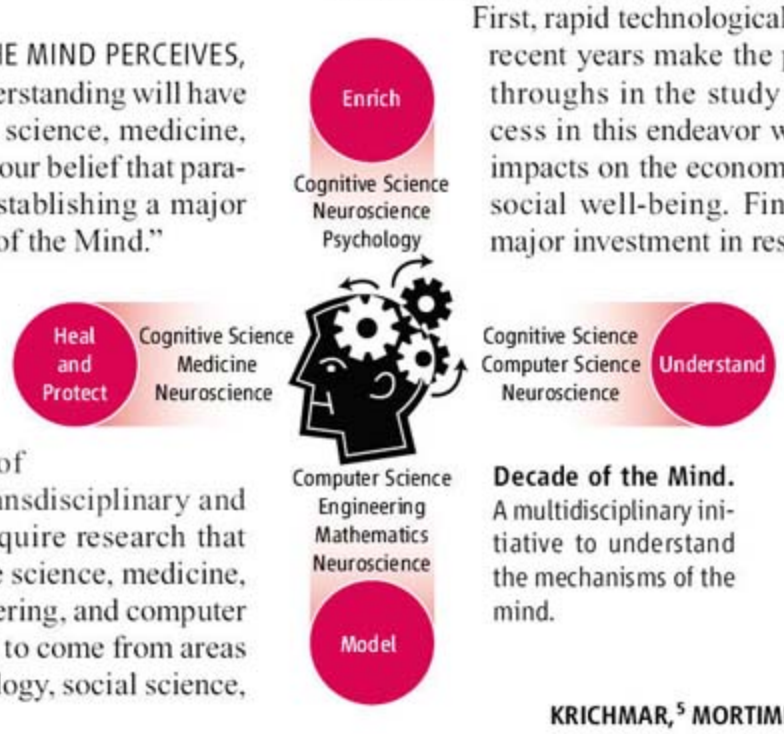
1) Healing and protecting the mind. Disorders of the mind affect more than 50 million Americans annually at costs exceeding $400 billion (*2*). It is our obligation as scientists and health care workers to address these social, personal, and economic burdens on our society.

2) Understanding the mind. Although much progress has been achieved recently in brain research, a fundamental understanding of how the brain gives rise to the mind is still lacking. Knowledge of the mind's inner workings will require new tools that can deeply probe mental processes. Research should be encouraged on aspects of the mind believed to be uniquely human, such as the notion of self, rational thought processes, theory of mind, language, and higher order consciousness.

3) Enriching the mind. A better understanding of the mind will enrich our lives by improving our education system at all levels, treating mental illnesses and addictions, extending the mind to new skills, and educating the general public on legal and ethical issues involving the brain and the mind.

4) Modeling the mind. Combining theoretical and computational methodologies with empirical findings will be crucial for healing, understanding, and enriching the mind. Large-scale brain modeling efforts will predict and diagnose disorders, test treatments for diseases, explain brain and mind phenomena, spur development of novel computing architectures, and enable the construction of intelligent machines.

Why is a national Decade of the Mind initiative necessary now? First, rapid technological and biomedical progress of recent years make the present time ripe for breakthroughs in the study of the mind. Second, success in this endeavor will have broad and dramatic impacts on the economy, national security, and our social well-being. Finally, to achieve success, a major investment in research and development will be required, with a time horizon on the order of 10 years. A Decade of the Mind initiative could achieve these goals and improve our lives and our children's lives in ways we cannot now conceive.




**Decade of the Mind.** A multidisciplinary initiative to understand the mechanisms of the mind.

JAMES S. ALBUS,[1]* GEORGE A. BEKEY,[2] JOHN H. HOLLAND,[3] NANCY G. KANWISHER,[4] JEFFREY L. KRICHMAR,[5] MORTIMER MISHKIN,[6]† DHARMENDRA S. MODHA,[7] MARCUS E. RAICHLE,[8] GORDON M. SHEPHERD,[9] GIULIO TONONI[10]

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*The views expressed in this article do not necessarily represent the views of the U.S. National Institute of Standards and Technology, the U.S. Department of Commerce, or the U.S. government.

†This Letter was prepared as part of the co-author's official duties as a U.S. government employee. The views expressed in the Letter do not necessarily represent the views of the NIMH, NIH, DHHS, or the U.S. government.

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2. J. Carey, Ed., *Brain Facts: A Primer on the Brain and Nervous System* (Society for Neuroscience, Washington, DC, 2006).
3. The authors represent the steering committee for the Decade of the Mind initiative. A Decade of the Mind Symposium was held on 21 to 22 May 2007 at The Krasnow Institute for Advanced Study at George Mason University in Fairfax, VA, where many of the issues contained in this Letter were originally discussed.

## Clarifying Cougar Management in Oregon

I AM CONCERNED THAT V. MORRELL'S *SCIENCE* Now article "Oregon cougars to be hounded" (http://sciencenow.sciencemag.org/cgi/content/full/2007/629/2; posted 29 June) may lead readers to misconstrue how the passage of the new law, HB 2971, affects cougar management in the state.

HB 2971 does not "bring back hound-hunting" or "overturn" Measure 18, which was enacted by Oregon voters in 1994. The new law simply clarifies some of the ambiguity in the original Measure 18.

Measure 18 specifically allowed the Oregon Department of Fish and Wildlife (ODFW) to use "agents" to manage cougar populations, and ODFW did so in the initial years after the measure was passed. But the Department of Justice later determined that it was not clear that ODFW had legislative authority to appoint agents. HB 2971 simply makes it clear.

The photo caption used with the article states that "citizens" can now use hounds when hunting cougars. Sport hunters still cannot use hounds. Only agents selected, trained, and supervised by ODFW will be authorized to hunt with hounds, and only when they are acting in official capacity to implement cougar management.

**CLAIR KUNKEL**

Acting Deputy Director, Oregon Department of Fish and Wildlife, 3406 Cherry Avenue, NW, Salem, OR 97303, USA.

## Characterizing Health Risks

IN THE REPORT "A COMMON VARIANT ON chromosome 9p21 affects the risk of myocardial infarction" (8 June, p. 1491; published online 3 May), A. Helgadottir *et al.* use relative risks to describe an association between myocardial infarction (MI) and a common sequence variant on a specific chromosome. They conclude that individuals in the population homozygous for this variant have an estimated 1.64-fold greater risk of suffering MI than noncarriers and a 2.02-fold risk for early onset MI cases. Although calculating relative risks and relative risk reduction is widely used to represent experimental results, great care needs to be taken when reporting, interpreting, and characterizing health risks and benefits based primarily on relative risks.

The authors appear to allude to this issue in the last paragraph of their Report by stating: "However, as the relative risks are not extremely high, it explains only a small fraction of the familial clustering of the disease and would not generate large linkage scores." This cryptic sentence, however, falls far short of acknowledging that an understanding of absolute risks, absolute risk reduction, and the number needed to treat will be a necessary prerequisite to making informed decisions on medical intervention.

There is general agreement in the scientific community that the exclusive use of relative risks distorts and often grossly exaggerates the significance of health risks and benefits (*1*–*4*). Absolute risk values provide information essential to physicians and patients alike. For example, hypothetically, an absolute risk analysis could show that 2 individuals out of 10,000 with the variant get heart disease and 1 individual without the variant gets heart disease. In this case, the absolute risk reduction would be 0.01%, 10,000 people would have to be treated to observe 1 benefit, and 99.99% of people with the variant would not benefit from intervention. The increased relative risk for individuals with the variant, in this hypothetical example, would be 100%, a much more impressive number.

The public hears about health risks and benefits from many sources on a daily basis. Although many approaches may be scientifically legitimate, the misinterpretation of statistical relationships can lead to inappropriate risk management decisions. The scientific community and the public would have been better served if limitations regarding the relevance and importance of this Report's findings were more clearly articulated.

**ERIK RIFKIN[1]* AND EDWARD BOUWER[2]**

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*The author is president of a private company specializing in risk assessment.

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### Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 3 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

## Response

RIFKIN AND BOUWER FOCUS ON THE ABSTRACT of our paper, where we summarized the effect of the discovered variant by giving its estimated relative risk, something that is relatively standard when reporting results of this sort. We cannot see how our statement that "individuals in the population homozygous for this variant have an estimated 1.64-fold greater risk of suffering MI than noncarriers" "grossly exaggerates the significance of health risks and benefits." Not only do we believe relative risk to be a very relevant parameter, it is also what our study design allows us to estimate directly and, hence, the appropriate value to highlight in the abstract.

The Letter gives a hypothetical example where the relative risk is twofold, but the absolute increase in risk is low, presumably to highlight that here the effect is trivial. Although the latter might hold in some cases, it is far from being true in general. Consider a more concrete example. The chance of a fatal plane crash with a major commercial airline is so small that, even for a frequent flier, the lifetime chance of being involved in a fatal accident is still very small. The latter remains small even when multiplied by five, but most people will probably agree that it is a serious matter if the chance of a fatal plane crash is suddenly increased fivefold. Return to our manuscript and MI, a rather more common occurrence than a plane crash. The "cryptic sentence" Rifkin and Bouwer refer to was meant to address a more subtle issue than the difference between absolute and relative risks. Population attributable risk (PAR) of a genetic variant for a disease is defined as the fraction of cases that would be eliminated from the population if the risks of the carriers were to be reduced to that of the noncarriers. That the discovered variant has an estimated PAR of 21% for MI in general makes its impact substantial from a public health point of view. But PAR is not the appropriate measure of the contribution of a variant to the familial clustering of the disease; it is better measured by the sibling recurrence risk ratio, $\lambda_s$. In particular, if two variants have the same PAR, then the one that is less frequent but has a higher relative risk will have a higher $\lambda_s$. Also, PAR is not additive when multiple variants are considered; mathematically, there could be 10 independent variants, each with a PAR of 50%. The point we tried to make is that, although the discovered variant has a PAR of 21% for MI, it does not mean that it accounts for 21%

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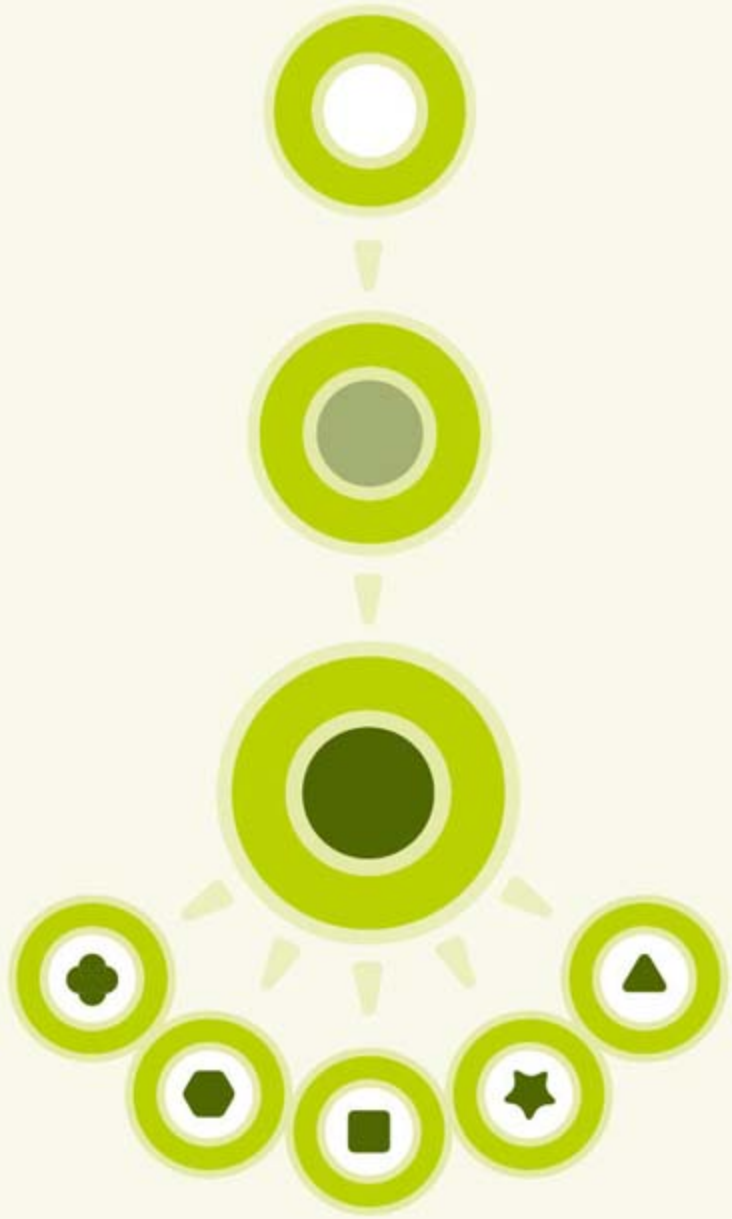

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of the genetic component to the disease. However, even though PAR and $\lambda_s$ are distinct measures, they are both calculated using relative risk instead of absolute risk.

**KARI STEFANSSON AND AUGUSTINE KONG**

deCODE genetics, Sturlugata 8, IS-101 Reykjavik, Iceland.

## Interpreting Sequences from Mastodon and *T. rex*

J. ASARA *ET AL.* REPORTED THAT COLLAGEN proteins from well-preserved ancient fossil bones from a 160,000- to 600,000-year-old mastodon and a 68-million-year-old *T. rex* can be extracted and sequenced ("Protein sequences from mastodon and *Tyrannosaurus rex* revealed by mass spectrometry," 13 April, p. 280). Tandem mass spectrometry (MS/MS) is an effective sequencing method for ancient fossils when DNA is not available. It has come to the original authors' attention that there are concerns regarding the reported sequences containing glycine (G) hydroxylation, as well as some positions of proline (P) hydroxylation. Although nonstandard postmortem modifications are possible (*1*) and the spectra suggest glycine as a potential hydroxylation site, we acknowledge alternative interpretations that are consistent with our spectra, the structure of collagen, and previous collagen research since α-hydroxyglycine has been reported to be unstable (*2*, *3*).

Ion trap mass spectrometers scan very fast and are highly sensitive but cannot resolve amino acids or combinations of modifications and amino acids that are near isobaric (same nominal mass), as stated in the original Report. It is sometimes difficult to determine the precise position of a modification from adjacent or nearby amino acid residues, since MS/MS spectra often lack sufficient site-specific fragment ions (*4*).

Hydroxylation of P to 4-hydroxyproline is a highly abundant modification that stabilizes the triple helical structure of collagen. Hydroxylation also occurs to a lesser extent on lysine (K) residues (*5*, *6*). In type I and type II collagens, these hydroxylation sites have been reported to exist nearly exclusively for P or K in the Y position of the collagen triplet repeat –GXY- (*7*, *8*). A singular exception, one P in human collagen I and II, is X position hydroxylated to 3-hydroxyproline (*9*). For several spectra, we determined that G was hydroxylated when an alternative interpretation based on the same spectra could accommodate the more likely Y position. In another situation, we could not differentiate between isoleucine (I)/leucine (L) and hydroxylated proline, P(OH) (nominal mass of 113 Da with an exact mass difference of 0.0364 Da). Serine (S) residues adjacent to or near unmodified proline -SP- could be interpreted as alanine (A) in place of serine adjacent to hydroxyproline -AP(OH)- with the same nominal mass of 184 Da. Alternatively, –G(OH)A- could be interpreted as –GS-. Deamidation of asparagine (N) or glutamine (Q) is a posttranslational modification resulting in an amino acid mass increase of 1 Da to aspartic acid (D) and glutamic acid (E), respectively, and could not always be distinguished due to the ion trap's resolution and mass accuracy. We have determined that one of the reported *T. rex* spectra for the peptide GLVGAPGLRGLPGK is statistically insignificant when searched against large protein databases and is a low confidence sequence, while the other six *T. rex* sequences remain high confidence. Since all sequences

matched to a single bone protein family when searched against the all-taxon NCBI nonredundant protein database containing more than five million entries, rates of false positive identification were very low.

Surprisingly, a likely alternative interpretation leads to the unique *T. rex* peptide sequence GAPGPQGPSGAP(OH)GPK. Alternate interpretations for the collagen sequences reported in the original manuscript are available in the Supporting Online Material (*10*), the sequences for mastodon and ostrich (not originally published) appear in UniProt Knowledgebase, and the complete list is being placed in a supplementary repository (ftp://ftp.ebi.ac.uk/pub/databases/supplementary). These alternate sequences strengthen our assertion that collagen has been sequenced from ancient fossil bones without contradicting well-established structures for collagen modifications. In retrospect, prior knowledge of collagen structures would have helped to construct our peptide library; however, the oversight inadvertently provides us assurances that genuine collagen sequences were detected.

Overall, these possible minor sequence alterations do not alter our original conclusions that ancient collagen peptides were sequenced from well-preserved mastodon and *T. rex* fossil bones, and that *T. rex* sequences match better to chicken than any other single organism of currently known sequence. For future sequencing efforts, ultra–high-resolution Fourier transform or Orbitrap mass spectrometry technology will be used for acquiring precise masses and distinguishing near isobaric amino acids (*11*).

**JOHN M. ASARA,[1,2] JOHN S. GARAVELLI,[3] DAVID A. SLATTER,[4] MARY H. SCHWEITZER,[5] LISA M. FREIMARK,[1] MATTHEW PHILLIPS,[1] LEWIS C. CANTLEY[1,6]**

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12. J.M.A. acknowledges B. Brodsky for helpful discussions. J.S.G. and D.A.S. acknowledge N. Kelleher and K. Lilley for helpful discussions and P. Browne for assistance in preparing the UniProt entries.

## CORRECTIONS AND CLARIFICATIONS

**Reports:** "The Release 5.1 annotation of *Drosophila melanogaster* heterochromatin" by C. D. Smith *et al.* (15 June, p. 1586). The affiliation for ShengQiang Shu and Christopher J. Mungall was listed incorrectly. They are affiliated with Berkeley Bioinformatics and Ontologies Project, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA. In addition, two funding sources were omitted from the acknowledgements note. The work in this paper was also supported by NIH grant P41 HG000739-15 (S.S.) and by the Howard Hughes Medical Institute (C.J.M.).

**Special Issue on Sustainability and Energy: Perspectives:** "Ethanol for a sustainable energy future" by J. Goldemberg (9 February, p. 808). There are numerical errors in Table 1. Under the heading "Geothermal energy," the value for "Total" should be 1.08, and the value for "Heat" should be 0.80.

BEHAVIOR

# The Social Origin of Mind

**Alison Jolly**

*He who understands baboon would do more towards metaphysics than Locke.*
—Charles Darwin, Notebook M (1838).

Imagine as a life's work toting loudspeaker, tapes, batteries, and video camera around the Okavango Delta, occasionally being treed by lions or warned off by elephants. You skulk into long grass to conceal the speaker, then wait and wait until the supposed author of the playback call is safely out of sight and the intended hearer facing at least 90° away. It may take you a whole year to complete one series of experiments—all with the goal of confusing a baboon.

*Baboon Metaphysics* is the distillation of a big chunk of academic lives: the wife-and-husband team of Dorothy Cheney and Robert Seyfarth plus a flock of their students and friends. It is exactly what such a book should be—full of imaginative experiments, meticulous scholarship, limpid literary style, and above all, truly important questions. Baboon confusion turns out to be one of the strongest tools available for illuminating a primate's metaphysics as well as our own. What are the components of intelligence? How does intelligence evolve to meet the challenge of life in a social group? Is behavioral foresight possible without real empathy and without a "theory of mind"? How can factual information be communicated without language? Can we impute consciousness to another species? Philosophers argue in the abstract; Cheney and Seyfarth offer data.

**Baboon Metaphysics**
The Evolution of a Social Mind

***by Dorothy L. Cheney and Robert M. Seyfarth***

University of Chicago Press, Chicago, 2007. 358 pp. $27.50, £16. ISBN 9780226102436.

The "social intelligence hypothesis" proposes that the major influence in the evolution of primate intelligence has been the challenge of life in a social group. Of course an environment of fruit trees, floods, and lions has its own challenges, but dealing with the environment is always mediated by society. Primates may not be as unique as we would like to believe: dolphins, dogs, and pinyon jays have many of the capacities of a baboon. It becomes clear, though, that human minds are fundamentally those of a social primate. Baboons offer insight into how we arrived at our own kind of mind.

**Cacma baboons (*Palio hamadryas ursinius*) in the Okavango Delta, Botswana.**

First and simplest, every baboon knows the voices of everyone in the 80-strong troop. Each call is tagged with the individual's identity. If the playback calls sound like an ordinary social interaction, the hearer is little interested, but if calls violate expectations she will look toward the speaker for much longer. If she assumes that a call has something to do with herself, she changes her behavior toward the supposed caller. Long suites of logically constructed experiments make it clear that baboons categorize others by both rank and matriline: these are rule-governed classes on separate axes. Baboons foresee others' behavior with great sophistication. However, they seem to lack empathy toward others' emotions or awareness of others' knowledge. Cheney and Seyfarth write: "Baboons' theory of mind might best be described as a vague intuition about other animals' intentions.... There are hints that learned contingencies alone cannot explain all aspects of baboon behavior, but we cannot yet conclude that baboons regard other baboons—even tacitly—as intentional beings with goals, motives, likes, and dislikes."

Are baboons self-aware? Baboons distinguish clearly between "me" and "not-me" as the recipient of a playback call. They identify strongly with their own matriline. They join alliances with their own kin, but also they may approach and reconcile with animals their kin have threatened, apparently on behalf of the threatener. "In between-family fights, the baboon's 'I' expands to include all of her close kin; in within-family fights, it contracts to include only herself. This explanation serves for baboons as much as for the Montagues and Capulets." For a baboon to place herself within the group's social network, "she would seem to need some image of herself as a unique social being, distinct from all others and characterized by a unique set of social relationships with particular others."

Cheney and Seyfarth note several aspects of the "syntax of social knowledge." Knowledge conveyed by a vocalization is representational, that is, highly specific about a particular sort of predator or about a particular individual. Social knowledge has discrete values: a move grunt is not an infant grunt. It is hierarchically structured (I would rather say categorized) according to rank, matriline, and other attributes of the call-giver. It is rule-governed and open-ended, leading to "a cognitive system that allows animals to comprehend a huge number of messages from a finite number of signals. If a baboon understands that *Sylvia threat-grunts and Hannah screams* [life as usual] carries a different meaning from *Hannah threat-grunts and Sylvia screams* [Shock! Horror!], she can make the same judgement for all possible pairs of individuals in the group, including any new individuals who may join." Lastly, knowledge is propositional and independent of sensory modality. The knowledge obtained from playbacks alone is similar to actually seeing an interaction. This allows interpretation of sounds as a dramatic narrative: "Sylvia is threatening Hannah and causing her to scream."

The authors conclude that the syntactic properties of language originated in the structured knowledge necessary for a highly social primate. One widely quoted view of language origins is that proto-language, like pidgin dialects, lacked syntax (*1*). On the contrary, argue Cheney and Seyfarth, a propositional interpretation of calls in our own ancestors must have preceded the evolution of human language.

Humans, even very young children, are

CREDIT: KEENA SEYFARTH/FROM *BABOON METAPHYSICS*

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unlike all other primates in our urge to share knowledge and (except for autists) our huge empathy with others. Cheney and Seyfarth embed the evolution of language deeply into human "theory of mind" along with tool use and our eventual conquest (or disruption) of the environment. In this view, social intelligence was what got us to being as bright and complicated as baboons—and what has taken us still further, into becoming humanity.

I might suggest, though, that there is a brand new evolutionary pressure in the Okvango Delta: outwitting alien scientists. Watch out for Sylvia's Okavango Troop if they ever catch on to Cheney and Seyfarth!

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10.1126/science.1144284

HISTORY OF SCIENCE

# The Productivity of Prediction and Explanation

**Matthew L. Jones**

Isaac Newton famously eschewed "framing hypotheses" about the causes of gravity in favor of demonstrating a mathematical relation common to free fall on Earth and the motion of celestial bodies. Newton's refusal to explain the nature of gravity dismayed many contemporaries, who saw him as sacrificing the intelligibility of the world for mathematical prediction of effects. Newton's mathematical account of gravity became a model for a new kind of scientific intelligibility, one where empirically grounded and predictive mathematical accounts of the relations among things were preferred to causal, but empirically underdetermined, explanations. Accepting Newton meant appreciating how his mathematically framed and empirically justified generalizations might provide the best account of the world we can have—the best kind of sense we can make of the world.

Recent debates over the value of string theory underscore how central the contest among different ways of making the world intelligible remains in modern science. Such debates involve the very definition of science, the proper activities of its practitioners, and concrete questions about who ought to be funded and hired, and who not. Written for a nonspecialist audience, Peter Dear's *The Intelligibility of Science* argues that such prescriptive debates within science are integral to its development. The classic story of Newton provides the early turning point in Dear's concise and ambitious essay. Ranging from Aristotle and Lavoisier to Maxwell and Darwin and from Descartes to Einstein and Bohr, Dear portrays the development of modern science through the shifting accounts of what it means to make nature intelligible.

**The Intelligibility of Nature**
How Science Makes Sense of the World

***by Peter Dear***

University of Chicago Press, Chicago, 2006. 254 pp. $27.50, £17.50. ISBN 9780226139487. Science.Culture.

Dear (a historian of science at Cornell University) distinguishes science as natural philosophy, an account of what the world really is and how it works, from science as an instrumental tool, a collection of techniques useful for making predictions about the world and for changing it. This division draws upon perhaps the oldest chestnut of the philosophy of science, the debate between realism and instrumentalism. Dear illustrates that a productive, unresolved, ever-changing tension between realist and instrumental aims best characterizes the distinctiveness of modern science, its epistemic and instrumental efficacy, and its social and intellectual authority.

It is easy to recount the history of science after Newton as something like a long series of attempts to restrain the use of the imagination and the production of overly clever explanations. In such a view, science depends on the sober consideration of data, not the creation of speculative accounts that could conceivably explain that data. More true to the diversity of scientific effort, Dear's account tacks between advocates of great empirical restraint and advocates of greater imaginative flight in causal explanation. Dear shows the importance of a certain will not to know, or rather, a will not to attempt to know the real nature of things in the development of numerous scientific disciplines. He likewise shows the importance of resistance to such epistemic modesty. For every Lavoisier who counseled against speculation about causes in favor of a focused collection of the physical relationships revealed through painstaking experimentation, there was a Priestley who insisted on attempting to know about the things themselves; for every Newton eschewing hypotheses, a Cartesian insisting on their importance. Science benefited from, indeed was constituted by, this ever-unresolved contest over the intelligibility appropriate to learning about and manipulating the natural world. Just as much creative and productive 18th-century science came from abandoning a quest for causal, mechanical models, much creative and productive 19th-century science involved searching for sufficiently sophisticated models.

As Dear covers many fields in a few pages, historians and philosophers will have some qualms. The starting point of the narrative comes a bit late and too far to the west: the enormously fruitful debates over the status of the physical and predictive in Islamic astronomy, which found their way to Nicolaus Copernicus, deserve some discussion. The instrumental turn in 17th-century natural philosophy likewise had deeper roots in alchemy and chemical practice, with a particular Aristotelian sanction, than found in this account. A slightly more formal and detailed exposition about the sort of intelligibility offered by the new mathematical tools of Newton and Maxwell, designed to fit, capture, and illuminate the phenomena of natural world, would enhance Dear's case.

Dear's position rests on a historically informative blurring of the category of instrumentality. His instrumentality includes both a narrow sense, the predictive powers of a theory, and a broader one, the capacity of a scientific theory (and its associated experimental techniques and apparatus) to change the world. Dear well demonstrates that two aspects of instrumentality were and remain muddled in modern science. Studies developing his position should closely track the changing interactions of these two instrumentalities with the demands of intelligibility.

Dear weaves together a great deal of academic history of modern physics, chemistry, and biology into a concise, coherent, and original narrative that is introductory without ever being superficial. Readers will come away both with a narrative of some highlights of scientific development and an illuminating argument underlying that narrative, a potent way of thinking about modern science more generally. Philosophically minded readers will be inspired to seek a more formal account of intelligibility than appropriate here; historically minded ones a deeper inquiry into the contingencies and details necessarily omitted. All will be guided by the insightful and up-to-date bibliographic essay.

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SCIENCE AND SOCIETY

# On The Road to Academic Greatness—A Parable

Don't underestimate the power of greed in the halls of science.

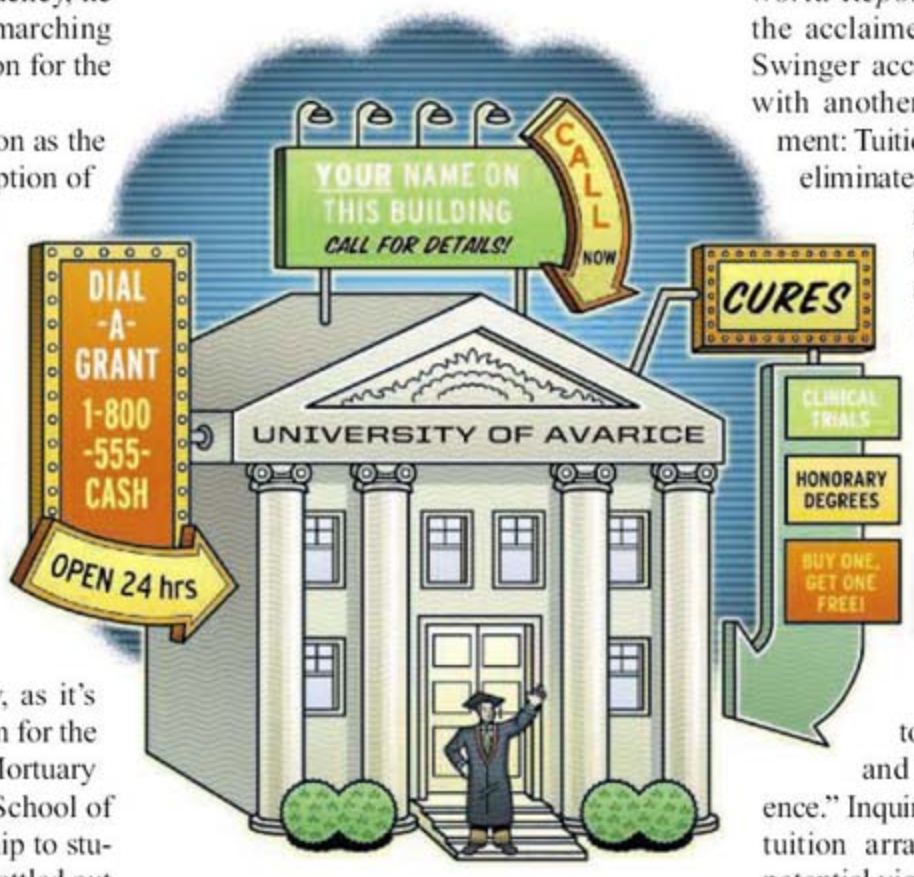
**Daniel S. Greenberg**

The swift ascent of the University of Avarice from obscurity to prominence was a seminal event of higher education in the second decade of this century. The transformation was the work of an innovative leader in university affairs, Dr. Grant Swinger. As provost of a leading university, Swinger had long been prized by academic headhunters. Offered the Avarice presidency, he promptly accepted and received marching orders to achieve national recognition for the little-known institution.

Renowned in his previous position as the founder of the Center for the Absorption of Federal Funds, Swinger brought to the challenge boldness, acumen, and energy. Confident and decisive, he inspired trust through his leadership abilities and scholarly attainments. Early in his career, he was the recipient of the prestigious Ripov Prize, annually awarded to the principal investigator holding the most concurrent grants. Other honors established him as a high achiever in the linkage of science and academe.

Before Swinger's arrival, U Av, as it's known, had briefly attracted attention for the body parts scandal at its School of Mortuary Science, which partnered with the School of Business in teaching entrepreneurship to students and faculty. The episode was settled out of court in an agreement that provided unspecified payments to bereaved relatives. (By agreement of the parties, court records were sealed, but this did not prevent a supermarket tabloid from reporting the case in an article titled "On the Trail of Granny's Femur.") Otherwise, U Av existed in an academic nether zone, along with numerous institutions that never register on the popular charts of university rankings.

Barely settled into office, Swinger made national headlines by announcing a record-breaking fund-raising goal, an astonishing $10 billion. The figure was more than double the previous high mark, set by Stanford, a renowned magnet for donations. Swinger told a press conference that the money would be "invested in excellence to meet the challenges that confront our nation and the world." Appointment of "distinguished faculty and concentration on urgent national problems" would have priority. He also disclosed that U Av would terminate employment of adjunct teaching staff "because of the financial and professional insecurity of their positions." Replacements would come from the graduate students' ranks, "thus providing the next generation of academics with valuable teaching experience."




The *New York Times* reported Swinger's announcements in an article headlined "Upstart U Reaches for the Stars—and the Big Bucks." Inquiries about the progress of the fund-raising drive were declined by U Av's rapidly expanding Office of Public Affairs as "premature, incompatible with privacy regulations, and potentially harmful to promising discussions with prospective donors."

U Av next came to public attention with an announcement of record-breaking tuition and fees—$100,000 per academic year, surpassing the prices of the brand-name schools. Applications for admission soared, earning the heretofore obscure institution its first notice in the coveted rating of *U.S. News & World Report*. "Hot newcomer" reported the acclaimed bible of academic rankings. Swinger accompanied the tuition increase with another headline-winning announcement: Tuition would not only be reduced or eliminated for students from families with modest incomes, but for the seriously impoverished, the university would provide payments to the students' families to compensate for earnings they might have provided. "We must be cognizant of today's economic realities," Swinger explained. NBC [the National Broadcasting Corporation] hailed Swinger as "the bold leader of a new generation of academic statesmen, visionary in outlook, sensitive to individual and national needs, and determined to make a difference." Inquiries about implementation of the tuition arrangements were dismissed as potential violation of privacy regulations.

The second year of the Swinger presidency brought another innovation to U Av—the founding of a major research facility, the Hugo First Institute for Human Experimentation, designed, Swinger explained at a ground-breaking ceremony, "to focus on 'translational research,' the formidable gap between basic science and bedside treatment." Noting that NIH had assigned a high priority and significant support for this type of research, Swinger vowed that the new institute would be "a leader in assuring the efficacy and safety of new treatments for the American people." Referring to Institutional Review Boards (IRBs), Swinger observed that "as often as they protect patients, they also get in the way of medical progress and constructive relations between academic institutions and industrial organizations. At U

CREDIT: PETER HOEY

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Av," he said with a flourish, "IRB stands for something else: Here, it means 'Industrial Research Buddy.'" Buttons and T-shirts bearing those words were distributed to all laboratory staff, and a similarly inscribed banner was hung on the biochemistry building. The *Wall Street Journal* editorialized that "the refreshingly straight-talking Dr. Swinger looks like a good prospect for taking the helm of the benighted FDA [U.S. Food and Drug Administration] and steering it into the oblivion that it so richly deserves."

U Av's growing prominence took a still greater leap forward with an agreement with a major pharmaceutical firm that provided for company support of research in U Av's laboratories, clinical testing of the firm's products at the Hugo First Institute, and patent sharing of promising developments. Financial and other details were withheld from public disclosure, the partners explained, "in compliance with privacy regulations and the need to protect proprietary information in joint pursuit of therapeutic benefits for the American people." As was later revealed, Swinger became a paid consultant for the company and, along with several members of the institute, received stock options in the firm. For strengthening the linkage between research and commercialization, senior members of U Av's technology transfer office were given tenured professorships. Initially, U Av's pharmaceutical partnership went smoothly, resulting in several promising patents and spin-offs.

But then, from the teeming ranks of perpetually malcontent graduate students, postdoctoral fellows, idle former adjuncts, and other ingrates, several went public with a variety of grievances. Shielded by protections for so-called whistle-blowers, they risked nothing. The most damaging allegations contended that the Hugo First Institute routinely fabricated reports of clinical trials based on nonexistent experimental subjects; that, in rare cases when trials were conducted, "results" were written up before experimental drugs were administered; and that research papers reporting the fraudulent trial results were routinely prepared by the sponsoring firms and published under the names of U Av researchers. The complainants told tales of eradication of disappointing data and drug sales pitches at continuing medical education programs by U Av faculty on the company payroll.

Promptly pledging "full and complete transparency," Swinger announced creation of a "blue-ribbon, independent inquiry." Following several closed-door meetings, the inquiry concluded that the allegations were "wholly without merit." Data corroborating the finding would not be made public, Swinger explained, in conformity with privacy regulations and the need to protect proprietary information. To soothe feelings on campus, Swinger called for "an intergenerational dialogue concerning the new world of science," a move that won plaudits for leadership.

As controversies over the Hugo First Institute receded, a new difficulty arose. A student on work-study assignment in the U Av development office during the staff's lunch break answered a telephone inquiry from a reporter concerning progress toward the $10 billion fund-raising goal. The student, untutored in dealing with the press, helpfully explained, "They haven't gotten anything yet. They're complaining all the time"—comments that were published, with insinuations of setbacks in U Av's progress toward national standing. Calling a press conference, Swinger earnestly pointed out that "major fund-raising is not an overnight process, and is not amenable to penny-by-penny counting." Attempts to contact the student who had spoken injudiciously brought the response that she was "no longer on campus," while reporters were discreetly advised that further information might be obtained from the university's mental-health clinic.

Though the Swinger administration was deeply troubled by these adversities, the glow of success remained undiminished, leading the various published rankings of academic quality to post even higher rating for U Av. "Look out, Ivies," *U.S. News & World Report* declared. Grant Swinger had not achieved success by ignoring reality. U Av was taking on water, and he alone knew it. Thus, when a distinguished search committee approached him as a possible candidate for heading the new permanent National Commission on Scientific Integrity, Swinger didn't say no. Instead, citing the inviolability of his vow to shepherd U Av to national greatness, he expressed appreciation for the proffered position. When urged to consider the needs of the nation, he modestly noted his relatively brief tenure at U Av, telling the aroused recruiters, perhaps at another time. Now ecstatic about the man in their sights, the committee overcame his resistance. Expressing deep regret, Swinger informed the U Av trustees that "my sense of responsibility to the nation's scientific enterprise compels me to accept the challenge that has been thrust upon me."

Meanwhile, U Av's jilted trustees wondered: When all was going so well, why would their prize president jump ship? As a first step, they ordered an audit in expectation of finding a solid financial base that would help attract the next leader for the climb to national prominence. Alas, the auditors' report was bleak: the $10 billion campaign had not yet covered its expenses; applications for admission had indeed risen, but in the absence of funds for financial aid, enrollments were down.

Other difficulties emerged. Carrying their allegations to Washington, the aggrieved graduate students and others received a warm reception on Capitol Hill, leading to an investigation of the Hugo First Institute. Pending the outcome, NIH prudently froze all grants at the institute. At the same time, the firm collaborating with the institute, fearing for its reputation in the drug marketplace, invoked its contractual right to withdraw from the relationship, taking with it all intellectual property and several items of costly scientific apparatus. The firm's general counsel reminded his U Av counterpart that all dealings between the two organizations were protected by nondisclosure provisions.

Though busy at his new position, Swinger maintained a careful watch on events at U Av. Thus, he was not surprised by an urgent request to meet with the chairman of the commission's board of trustees. The meeting was brief and ended with the understanding that Swinger would be able to review the press release announcing his resignation.

At U Av, following a series of interviews, the trustees were particularly impressed by the professional credentials and demeanor of one candidate. In contrast to Grant Swinger's take-charge persona, she projected a calm self-assurance. Still recovering from the Grant Swinger experience, the trustees were especially reassured when, asked for her philosophy of governance, she thoughtfully reflected for a moment, and then replied: "Don't underestimate the power of greed in the halls of science or the wholesome presence of altruism and self-respect. And don't overlook shame and embarrassment as forces for good behavior in scientific affairs" (*1*).

The trustees reacted favorably to this sage formulation, though one of them fleetingly thought he had previously encountered those words, perhaps in a recent book. But he joined with his colleagues in offering the presidency to this outstanding candidate, who promptly and graciously accepted.

**Reference**

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10.1126/science.1148030

PLANETARY SCIENCE

# The Case of Saturn's Spin

Saturn's rotation period is shorter than previously thought, which may have important consequences for understanding how the giant planets formed.

**Morris Podolak**

Planet formation theorists, like detectives, have to gather clues and put them together to explain an event that happened in the past. Sometimes the clue is so subtle that it requires a chain of reasoning to see how it contributes to unraveling the mystery. As Sherlock Holmes said, "It has long been an axiom of mine that the little things are infinitely the most important" (*1*). The work reported by Anderson and Schubert on page 1384 of this issue is a case in point (*2*). These authors have found that Saturn rotates somewhat more quickly than had been thought. This apparently minor result may have profound implications for our understanding of giant planet origins.

The early solar system began as a gas disk around the Sun, and two scenarios for formation of the giant planets seem possible. One scenario, the core accretion hypothesis (*3*), argues that the solids in the outer solar system, in the form of planetesimals, were gradually accreted into a planetary core on the order of 15 Earth masses. Such a massive core could then attract a large amount of hydrogen and helium from the surrounding disk to form a gas giant planet. Although some of the core might be mixed back into the accreting gas as it collapsed onto the planet, we would still expect Jupiter and Saturn to have cores on the order of 10 Earth masses.

The other scenario, the disk instability hypothesis (*4*), argues that the gas disk itself was unstable and that density fluctuations became large enough that some portion of the disk collapsed under its own gravity. This collapsing clump would eventually evolve into a gas giant planet. Some of the solids that were in the gas would eventually settle into a core (*5*), but that core is expected to be small, on the order of a few Earth masses.

Although most theorists favor the core accretion scenario, both hypotheses have strengths and weaknesses. One possible way to resolve the issue is to investigate the structure of the two gas giants in our solar system. Are the cores of Jupiter and Saturn closer to 15 Earth masses or to zero? To answer this question, we have to model the internal structure and composition of these planets.

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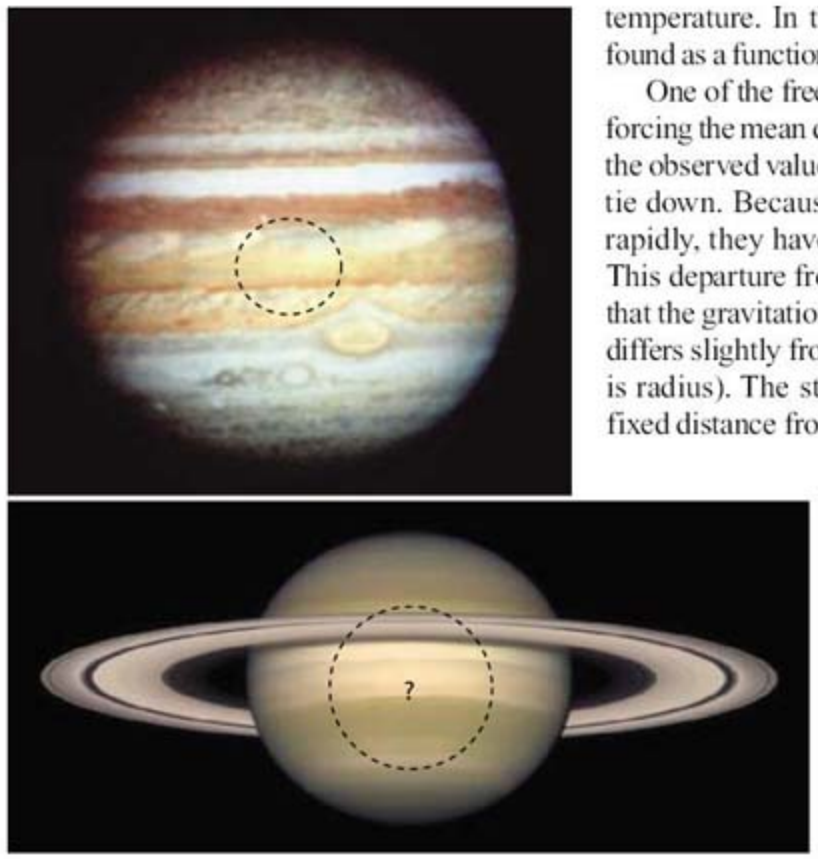


**Core issues.** Jupiter is three times as massive as Saturn, so the pressures in its interior are much higher than those in Saturn, and the material there is more compressed. As a result, Jupiter and Saturn have nearly the same radius. Here, the planets are shown at sizes relative to their uncompressed density to stress the difference in core mass. Thus, Jupiter (**top**) appears larger than Saturn (**bottom**), and Saturn's 20–Earth mass core (dotted circle) appears to have roughly 1.6 times the radius of Jupiter's 5–Earth mass core.

The standard approach is to assume a reasonable composition with some free parameters. Typically, one assumes that there is a heavy-element core of undetermined mass (one free parameter), surrounded by an envelope of hydrogen, helium, and some fraction of heavier material mixed in (a second free parameter). The details are not very sensitive to the exact choice of additional heavy material, but this too adds freedom in fixing the composition. The pressure inside the body can be computed by assuming that at each depth the pressure exactly balances the weight of the overlying layers. There is good reason to believe that the envelopes in Jupiter and Saturn are convecting, so that the temperature gradient follows an adiabat (i.e., a sequence of changes in pressure and temperature but with no heat exchanged). Thus, if the temperature at, say, the 1-bar pressure level is known, the temperature throughout the envelope can be determined. All that remains is to use the best physics available to determine the density of the material, given its pressure and temperature. In this way, the density can be found as a function of depth.

One of the free parameters can be fixed by forcing the mean density of the planet to match the observed value, but the others are harder to tie down. Because Jupiter and Saturn rotate rapidly, they have a pronounced oblateness. This departure from a spherical shape means that the gravitational potential of these planets differs slightly from the usual $r^{-1}$ law (where $r$ is radius). The strength of the potential at a fixed distance from the center will vary as the angle from the spin axis changes. The dependence on this angle is expressed by a series of coefficients called gravitational moments. These moments can be measured by following the motion of a satellite in the planetary gravitational field. They can also be computed from the internal density distribution and the rotation rate of the body.

Because of uncertainties in the composition and in the pressure-density relation at very high pressures, there are a number of "reasonable" density distributions that fit the observed parameters for Jupiter, and there is some ambiguity as to what the size of Jupiter's core really is. The evidence seems, however, to point to a core of between 0 and 5 Earth masses (*6*). This presents a difficulty for the core accretion hypothesis, but not for the disk instability hypothesis (*7*). The problem is with Saturn. The same models that predict a small core for Jupiter (with rather large error bars) predict a core of some 10 to 20 Earth masses for Saturn, and it is not at all clear why there should be such a large difference. Theorists have tended to set aside this piece of information because they are not sure how it fits into the whole picture.

Determining the rotation rate of a gaseous planet is difficult, and previous assessments were based on measurements of the magnetic field (*8*, *9*). On the basis of data from the Cassini, Pioneer, and Voyager missions, Anderson and Schubert argue convincingly that Saturn's rotation period is about 7 minutes

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less than the earlier value. This faster rotation rate means that to fit the observed gravitational moments, the internal density distributions computed for Saturn must be revised. The core mass will most probably be reduced, bringing it closer to that of Jupiter (see the figure). The extent of this reduction will depend on the details of the physics.

Saturn's mass is only one-third that of Jupiter's; thus, it is likely that the secondary processes that have been suggested to reduce the size of Jupiter's core in the core accretion scenario, or to form the core in the disk instability scenario, might be different enough between the two planets to explain the difference in the size of their cores. Perhaps we will even be able to use this information to help decide between the two hypotheses. Like Sherlock Holmes, I hesitate to speculate too much before having the facts. In view of this new data, planet formation theorists should sit up and take notice.


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10.1126/science.1147793

CELL BIOLOGY

# The Stress of Relaxation

Two modes of activation explain how an enzyme controls blood vessel responses to oxidative stress, hormones, and neurotransmitters.

**H. Criss Hartzell**

Oxidants and free radicals, according to the vitamin mongers, are the ruination of our existence. They include superoxides ($O_2^-$), hydroxyl radicals ($OH^-$), and peroxides ($H_2O_2$), collectively called "reactive oxygen species" (ROS). These molecular brigands—the by-products of mitochondrial metabolism—corrode molecules by snatching their electrons. They are blamed for causing cancer, heart disease, Alzheimer's disease, and old age (*1*). Yet in a reversal of the view that has dominated since the 1950s, we have come to appreciate that ROS play essential roles in healthy cell signaling. On page 1393 in this issue, Burgoyne *et al.* (*2*) show that oxidation activates a key enzyme that causes blood vessels to relax. This finding raises a paradox: Why, if oxidation can relax blood vessels, is oxidative stress associated with hypertension?

Vascular smooth muscle cells contract using filaments of actin and myosin molecules. Hormones and neurotransmitters control muscle tone by affecting the phosphorylation state of myosin (see the figure) (*3*, *4*). Vasoconstrictors, such as angiotensin II, increase the concentration of cytosolic calcium ions ($Ca^{2+}$), which activates an enzyme (myosin light chain kinase) that phosphorylates myosin. Also, an enzyme (myosin light chain phosphatase) that dephosphorylates myosin is inhibited. Vasorelaxants, such as acetylcholine, have the opposite effects. Protein kinase G (PKG) is a pivotal enzyme in vasorelaxation (*3*). The PKGIα isoform studied by Burgoyne *et al.* phosphorylates a panoply of substrates, ultimately decreasing myosin phosphorylation.

How is PKG activated by vasorelaxants? The best-understood pathway involves endothelial nitric oxide synthase (eNOS), which generates nitric oxide (NO). This gaseous molecule diffuses from the endothelium to vascular smooth muscle and activates cytosolic guanylate cyclase, thus triggering the production of guanosine 3′,5′-monophosphate (cGMP), which activates PKG. The new mechanism proposed by Burgoyne *et al.* involves oxidation-mediated PKGIα dimerization. The authors noted that $H_2O_2$ relaxes aortic rings and that relaxation correlates with dimerization (and hence, activation) of PKGIα. $H_2O_2$-mediated dimerization decreases the affinity of PKGIα for substrate, whereas cGMP-activation of PKGIα increases the maximum velocity of substrate phosphorylation. More importantly, Burgoyne *et al.* noted that $H_2O_2$ stimulates numerous downstream vasorelaxant events including decreased myosin phosphorylation. Thus, $H_2O_2$ is worthy of being an important relaxation signal.

Many proteins are affected by their redox states, but the physiological relevance is unclear, partly because high concentrations of oxidant are often used. Although tissue concentrations of $H_2O_2$ are not known, PKGIα is activated by 100 μM $H_2O_2$ (*2*), which is probably physiological. The best-documented targets for ROS are protein tyrosine phosphatases (*5*, *6*), whose enzymatic activity is abolished by oxidation of a cysteine residue in their active sites. This oxidation is stimulated by growth factors whose receptors trigger $H_2O_2$

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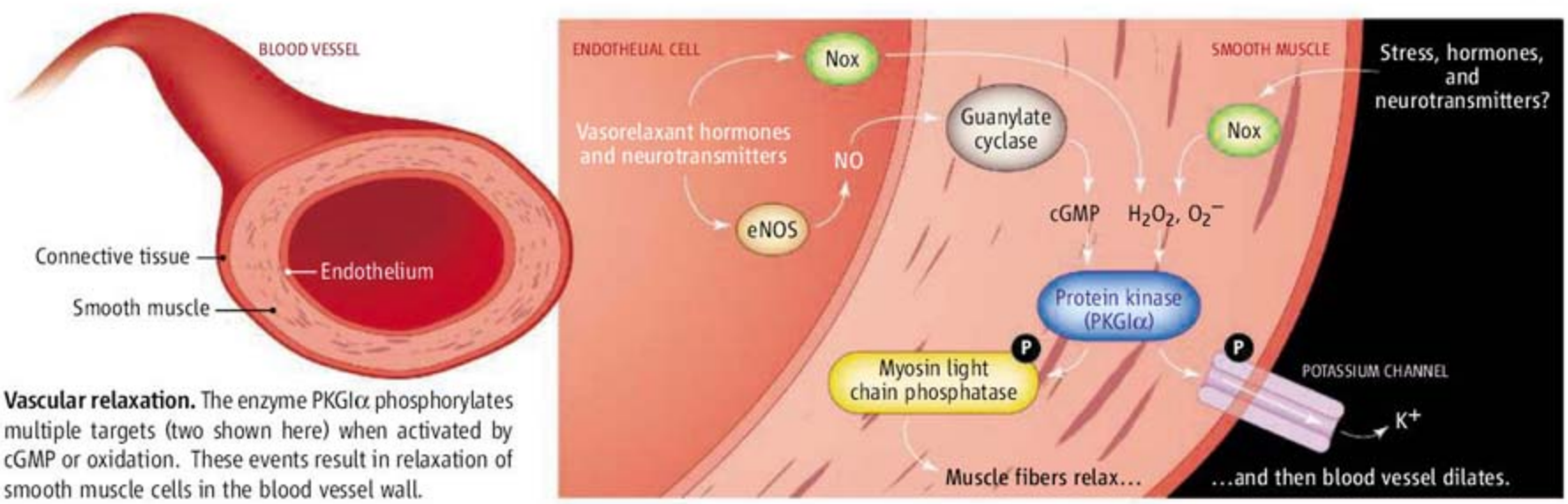


**Vascular relaxation.** The enzyme PKGIα phosphorylates multiple targets (two shown here) when activated by cGMP or oxidation. These events result in relaxation of smooth muscle cells in the blood vessel wall.

production via Nox [NADPH (nicotinamide adenine dinucleotide phosphate, reduced) oxidase] enzymes (*7*, *8*). The cysteine is susceptible to reversible oxidation because a nearby arginine lowers the $pK_a$ (acid dissociation constant) so that the cysteine is in the thiolate form. Interestingly, PKGIα $Cys^{42}$ is flanked by basic residues that might also lower its $pK_a$.

Endothelium-dependent relaxation involves several molecules besides NO. One of these, endothelium-derived hyperpolarization factor, relaxes muscle cells by opening $Ca^{2+}$-activated $K^+$-channels ($BK_{Ca}$). This hyperpolarizes the cell, causing voltage-gated $Ca^{2+}$ channels to close. It has been supposed that this relaxing factor may be $H_2O_2$ (*9*). The observation of Burgoyne *et al.* that PKG-mediated phosphorylation of the $BK_{Ca}$ channel is stimulated by $H_2O_2$ may strengthen the $H_2O_2$–endothelium-derived hyperpolarization factor link.

A major question is which vasorelaxants use $H_2O_2$ signaling. Burgoyne *et al.* show that insulin may use this pathway, but the amount of PKGIα dimerization is insufficient to fully explain insulin-induced vasorelaxation. Another question is which enzymes generate relaxant $H_2O_2$. Although Nox enzymes are the main source of ROS in the vasculature (*10*), Nox-produced ROS are associated with increased blood pressure, not vasodilation. Evidence points to angiotensin II as the chief culprit: Infusion of mice with angiotensin II stimulates Nox, increases ROS, and produces hypertension (*10*–*12*).

If ROS is associated with hypertension, how, then, can we explain the observation that $H_2O_2$ can produce vasorelaxation? There is a simple, but plausible answer: All ROS are not equal. Four different Nox isoforms are expressed in different subcellular locations in the vasculature (*10*), and produce ROS with different properties. Although Nox enzymes generate $O_2^-$, $O_2^-$ dismutates to $H_2O_2$. Compartmentalization is probably the key: Targets must be close to the site of $O_2^-$ generation, because $O_2^-$ has a fleeting lifetime and is membrane-impermeant; $H_2O_2$ targets are less restricted because $H_2O_2$ has a longer lifetime and is membrane-permeant. At least part of the vasoconstriction can be explained by destruction of NO by extracellularly generated $O_2^-$. By contrast, $H_2O_2$ may be generated within the muscle, conveniently located near its intracellular target, PKGIα.

There is also another way out of the paradox. Endothelial NOS can generate $O_2^-$ and $H_2O_2$ under certain conditions, resulting in vasorelaxation (*13*). This could provide a mechanism whereby the diffusible products generated by NOS switch between NO and $H_2O_2$. That, of course, raises the question of how the switch may be regulated.


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14. Supported by NIH grants EY014852 and GM60448.

10.1126/science.1148142


PHYSICS

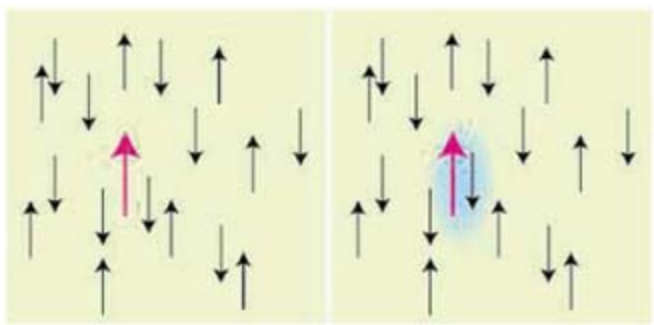
# Heavy Fermions in the Original Fermi Liquid

In some complex materials, the electrons appear to be unexpectedly heavy. Helium atoms show similar behavior in much simpler thin films of helium-3.


**Christopher A. Hooley and Andrew P. Mackenzie**


Physicists have long been fascinated by so-called heavy-fermion materials (*1*, *2*), in which the electrons act as though they had put on a lot of extra mass. Some of these compounds are also superconductors, so extracting the secrets of heavy fermions may yield insights into high–transition temperature superconductivity and other open questions. On page 1356 of this issue, Neumann *et al.* (*3*) report heavy-fermion behavior in an unexpected setting: two-dimensional layers of $^3$He adsorbed on a graphite surface. Their experiments raise the prospect of studying heavy-fermion physics in a quite different context, hopefully shedding new light on an old and fundamental puzzle.

The $^3$He atom is a fermion (that is, a quantum particle with half-integer spin, like electrons themselves). When gaseous $^3$He is cooled at atmospheric pressure, it liquefies at $T = 3.2$ K and remains liquid down to $T \approx 1$ mK, where it undergoes a superfluid transition (*4*). It is therefore unique in the periodic table: the only fermionic liquid at temperatures where quantum effects become important. Measurements of the properties of bulk liquid $^3$He in the 1950s revealed that the low-temperature behavior of the liquid was remarkably similar to that predicted theoretically for a gas of weakly interacting fermions. This is surprising, because at the densities of liquid helium, the interatomic interactions ought to be rather strong.



**The Kondo effect.** (**Left**) When a magnetic impurity (red arrow) is embedded in a Fermi liquid (quasi-particles represented by black arrows), it acts at high temperatures like a strong magnetic scatterer. (**Right**) At low temperatures, a spin singlet state forms with quasi-particles from the Fermi sea. This reduces scattering and incorporates the magnetic impurity electron into the heavy-fermion liquid.

This riddle was resolved by Landau (*5*–*7*), who argued that the reason for the similarity was that something was behaving like weakly interacting fermions—it just wasn't the original atoms. The "something" is now called a quasi-particle—a collective excitation that retains some of the properties of the original atom (e.g., it behaves like a spin-½ fermion) while having others modified (it can have a much different mass). The description of the residual interactions between these quasi-particles—which determine the properties of the liquid—was the vital ingredient of Landau's Fermi liquid theory.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Although originally developed for $^3$He, Landau's theory has made an even greater contribution to understanding electronic liquids in metallic solids. Its predictions account for the properties of a vast number of metals, but researchers have discovered in recent decades some special materials that, although metallic, do not conform to the theory. These have become known as non–Fermi liquids, and the possible origin of such states has become the subject of intense research (*8*).

One known source of non-Fermi liquid behavior is proximity to a quantum critical point (QCP). This is a point where the system undergoes a continuous zero-temperature phase transition, as a function of some nonthermal tuning parameter $p$ (which could be pressure, magnetic field, chemical doping, etc.) (*9*). Such transitions are often driven by competition between two types of interaction that favor different ground states, the balance between them being altered by tuning $p$. Around the QCP, in a region that can extend up to rather high temperatures, the properties of the metal are rendered anomalous by the presence of strong fluctuations between the competing states.

A much-studied realization of this phenomenon is in the heavy-fermion compounds (*2*). In these materials, f-electrons on rare-earth ions have a strong tendency to localize, while the remaining outer electrons form a conduction sea distributed throughout the material. Thus, the system is essentially a Fermi liquid interacting with localized spins, and two effects compete for dominance (*1*, *10*).

One is the Kondo effect, which occurs when the conduction sea screens the spin of each rare-earth ion as the temperature is lowered (see the figure). At low temperatures, the resulting state is a "heavy Fermi liquid"—a state that obeys Landau's theory, but with a quasi-particle effective mass up to a thousand times that of the bare electron.

The second competing interaction is the Ruderman-Kittel-Kasuya-Yosida (RKKY) effect. Neighboring spins interact via waves in the conduction sea, tending to make them align or anti-align depending on the details of the crystal structure. The resulting state is an ordered magnet, with the local moments on the rare-earth ions coupled only weakly to the conduction sea.

Neumann *et al.* report something truly remarkable: the observation of this competition, complete with QCP, in a system actually made from $^3$He atoms. They created a two-dimensional bilayer, with the upper layer playing the role of the conduction sea and the lower layer roughly that of the spins. In this case, coverage (the total two-dimensional density of $^3$He atoms in the bilayer) is the tuning parameter $p$. The low-coverage state appears to be a single-component Fermi liquid, analogous to the heavy Fermi liquid in the traditional case. The high-coverage state consists of two decoupled layers, one of which is in some way magnetic (*11*) while the other forms a Fermi liquid, analogous to the magnetically ordered state in the rare-earth version.

Although the main achievement of Neumann *et al.* is to bring non–Fermi liquid physics back to the prototype Landau system in $^3$He, perhaps the most intriguing feature of their data is an intervening phase that cuts in at coverages before the QCP is reached. This is tantalizingly reminiscent of the phases that mask QCPs in solid-state examples: superconductivity in several of the heavy-fermion compounds (*12*, *13*) and the as-yet-unidentified phase in $Sr_3Ru_2O_7$ (*14*, *15*). Many possibilities now exist for texturing and self-organization of correlated fermions at low temperatures. If characterization of this intervening phase can be accomplished, giving an example of novel phase formation in an uncharged atomic system, we will have taken another major step toward understanding the subtle physics that underlies a rapidly developing field.


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GEOCHEMISTRY

# "C"ing Arctic Climate with Black Ice


**Richard B. Alley**


New ice-core measurements suggest that soot influenced recent Arctic climate change.

Humans have put our sooty foot in a lot of places, leaving visible tracks with consequences. On page 1381 in this issue, McConnell *et al.* report a new way to see those tracks, finding them bigger, blacker, and more influential than we thought (*1*).

Climate scientists are now confident that business-as-usual fossil-fuel burning for another century or two would lead to substantial global warming in response to increased atmospheric carbon dioxide ($CO_2$) concentrations. However, it is more difficult to project the climate of the next decade, and it has only recently become possible to confidently attribute most of the changes over the past century to specific causes. This is because the $CO_2$ forcing of the past century, and the additional forcing of the next decade, are of the same order of magnitude as many other natural and human effects (*2*).

In particular, the effects of airborne particles (aerosols) introduce large uncertainties into climate-change attributions (*2*). Most aerosols cause net cooling, partially offsetting greenhouse-gas warming, but black carbon (or soot) tends to warm the atmosphere, especially by lowering the very high reflectivity of snow. The short-term reduction in warming achievable by reducing soot emissions may help to avoid dangerous human influence on the climate (*3*).

Has soot contributed to past climate change? In the early 20th century, the Arctic warmed more strongly than anywhere else on Earth (*4*); was this natural climate variability, or might human soot have contributed?


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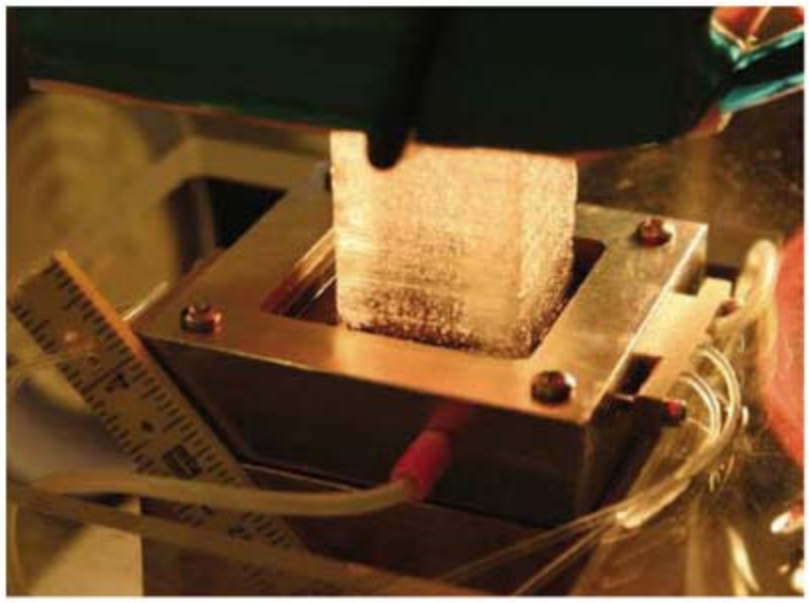
Unfortunately, modern instruments did not sample black carbon until recently. Investigators have relied on models and estimates of various combustion sources and efficiencies to constrain the effects of soot. McConnell *et al.* now report a detailed history of black carbon and its sources, extracted from a Greenland ice core, that goes a long way toward answering these questions.

A quiet revolution over the past decade has transformed many ice-core analyses. Once, trace chemicals in ice were determined by laboriously cutting, cleaning, and analyzing individual ice samples; now, clean melters feed streams of ice-core–derived water to a suite of instruments for continuous analyses. McConnell *et al.* used such an automated process (see the figure) to analyze a recently recovered core from a central-Greenland site where large amounts of snow accumulate every year. They obtained highly accurate, well-dated chemical histories—including black carbon concentrations—from 1788 to 2002, with a time resolution of less than a year.

For the first 60 years of the record, black carbon concentrations remained relatively stable, but the period from 1850 to 1951 showed highly elevated soot concentrations, especially during winter, when peak values were 10 times higher than the baseline. Lower values (although still higher than before 1850) mark the last 50 years of the record. Comparison to selected sections of a second core, collected 350 km to the south, shows close agreement, demonstrating the regional coherence of the signal.

Thus, black carbon concentration rose greatly to a peak in Greenland and still remains somewhat elevated. What was responsible? McConnell *et al.* were also able to detect low concentrations of organic molecules. They focused on vanillic acid, which originates largely from the burning of coniferous trees. Before 1850, soot and vanillic acid were highly correlated, especially during the summer fire season. Around 1850, when soot levels rose, correlation to the forest-fire indicator was lost, especially during winter. Instead, the higher soot values correlated closely with an acid-rain indicator (non–sea-salt sulfate, after exclusion of the well-known sulfate spikes from large volcanic eruptions). The human fingerprint is clear.

McConnell *et al.* even traced the soot to its source. Using the instrumental weather record for 1958 to 2002, they identified the main snowfall events for their site. Adopting a typical residence time for atmospheric particles, they then looked back along the trajectories of the precipitating air masses, finding the primary source region in eastern North America.



**History in the making.** A section of an ice core is melted in the clean laboratory for the report by McConnell *et al.*; meltwater from only the central part of the sample is diverted to the analytical line.

They infer a similar source for older samples by analogy, although circumstantial evidence points to increasing importance of an Asian source as North American emissions decreased after 1951.

Thus, a natural biomass-burning source of soot, primarily in summer, was overwhelmed by a fossil-fuel–burning source, primarily in winter, for a carbon-blacked century beginning about 1850. Since 1951, a weakening human signature may reflect technological advancement leading to cleaner combustion in eastern North America.

Do these observations help us understand climate history? Recent attempts to assess the climatic effects of black carbon, especially in the Arctic, have been largely restricted to the short interval of reliable instrumental records. McConnell *et al.* calculated the effect of their measured soot on absorbed solar radiation at their Greenland site. Based on comparison to an analysis for 1998 and 2001 for the whole Arctic (*5*), they then estimate the whole-Arctic effect of soot since 1788.

Changes in absorbed solar radiation are unimportant in the dark Arctic winter, and peak during early summer, before seasonal snow melts away to reveal darker surfaces less affected by soot. Focusing on that most sensitive season, McConnell *et al.* estimate an average Arctic warming effect from soot of more than 1 W/m$^2$ between 1850 and 1951, peaking in 1906 to 1910 at more than 3 W/m$^2$—eight times the natural forcing. For comparison, the globally and annually averaged forcing from the total anthropogenic $CO_2$ increase in the year 2006 was ~1.7 W/m$^2$ (*2*). For regional and seasonal changes, the soot effects must be important.

20th-century Arctic warming arrived in two sharp ramps (*6*): a late-century rise that paralleled the global response to greenhouse-gas increase, and a similarly strong early-century rise of more obscure origin. Processes in the Arctic, such as the ice-albedo feedback, tend to amplify natural variability (*7*) and the response to some forcing. The broad correspondence between the soot peak and the earlier observed warming suggests that the Arctic changes in this case may also be amplified, because the forcing was stronger in the Arctic than elsewhere.

Greenland is not the whole world, and more records (*8*) and modeling will be needed to establish whether soot was important in the early–20th-century Arctic warming. But the results of McConnell *et al.* place much tighter constraints on the history of soot forcing of Arctic climate and should reduce uncertainties in climate-change attribution. The rise and fall of soot in Greenland illustrate the human ability both to alter our environment and to limit those alterations.

The instrumental virtuosity and the richness of the ice-core record promise additional discoveries: today black carbon and vanillic acid, but what about tomorrow? At a recent meeting, I was asked whether big questions still remained to be solved in ice-core science. As shown by McConnell *et al.*, the answer is an unequivocal yes.

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**October 22, 2007**
**10 a.m. - 3:30 p.m.**

**Masur Auditorium**
**Warren Grant Magnusen**
**Clinical Center (Bldg. 10)**
**National Institutes of Health**
**Bethesda, Maryland**

Event is open to the public

| | |
|---|---|
| **Welcome** | Dr. Elias A. Zerhouni, Director<br>National Institutes of Health |
| **Opening Remarks** | Dr. Roger I. Glass, Director<br>Fogarty International Center, NIH |
| **Perspectives** | Dr. Ana Marusic, President<br>Council of Science Editors |
| **Presentations of Selected New Research** | Moderated by Dr. Catherine DeAngelis, Editor in chief, JAMA, and<br>Dr. Fiona Godlee, Editor in chief, BMJ |
| **Closing Remarks** | Dr. Donald Lindberg, Director<br>National Library of Medicine, NIH |

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INTRODUCTION

# Living in Societies

AN AWARENESS OF ONE'S POSITION AND THE RELATIONSHIPS OF OTHERS IN A group is a rarity among vertebrate species, yet it has proved so spectacularly influential in just one species—our own—that it has become a major factor in determining the ecology of an entire planet. Although we can describe behavior patterns and speculate about their evolutionary advantage, we also need to understand their contribution to a species' reproductive success. A new wave of research is investigating the primate social brain within this evolutionary context, often through studies of wild primates.

This special issue of *Science* explores the adaptive advantages of group life and the accompanying development of social skills. *Science*'s Greg Miller visited a chimpanzee sanctuary in Uganda to examine how researchers take advantage of these semiwild habitats to explore the cognitive abilities of our primate cousins (p. 1338). Just how valuable these opportunities can be is illustrated by the massive experimental study of physical and social cognition described by Herrmann *et al.* (p. 1360). Silk (p. 1347) describes how research on sociality in baboons and other Old World monkeys is beginning to reveal the long-term relationship between social bonds and the fitness of individuals. In their book *Baboon Metaphysics*, reviewed by Jolly (p. 1326), Cheney and Seyfarth further illustrate the value of field studies.

One of the most striking evolutionary trends among primates has been the expansion of brain size. Many competing theories have been invoked to explain this physiologically costly size shift. Dunbar and Shultz (p. 1344) review the evidence suggesting that it is the computational requirements of the special social lives of primates, in particular the requirement for pair bonding, that have driven the evolution of the human brain. An expanded capacity gives human beings unique cognitive skills, yet our primate cousins are quite capable of discriminating between necessary and superfluous actions, as described by Wood *et al.* (p. 1402). Our brains give us extraordinary powers of imagination and sophisticated cultural adaptation; for instance, humans can undertake mental time travel and anticipate the consequences of actions. Gilbert and Wilson (p. 1351) review the psychology and neuroscience of prospection; that is, how we predict future emotional experiences and how thinking about the future in the present can lead us astray. One of the most recent manifestations of our social brains has been the imaginative leap taken into the construction of virtual worlds. Our reporter Greg Miller undertook another field trip, this time to Second Life, and describes the progress researchers are making in using and understanding this new dimension of the human social experience (p. 1341).

It will be fascinating to learn how humans will cope with our increasingly virtual societies. We can only hope that our growing evolutionary insight into social behavior will help us to distinguish reasonable expectations of human society from those that are implausible.

**–CAROLINE ASH, GILBERT CHIN, ELIZABETH PENNISI, ANDREW SUGDEN**

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## Social Cognition

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Science

NEWS

# All Together Now—Pull!

**At wildlife sanctuaries, apes demonstrate their limits of cooperation, providing clues about the evolution of sophisticated social behavior**

NGAMBA ISLAND, UGANDA—Two chimpanzees, Baluku and Ndyakira, face a simple choice: Work together and reap a reward, or go it alone and get nothing. Residents of a sanctuary here, they could treat themselves to bowls of sliced bananas. But the fruit sits out of reach on a wood plank placed on the ground about a meter from their cage. To retrieve the fruit, they must each pull opposite ends of a rope rigged to the plank such that the ends are too far apart for either chimp to grab alone. Only with a coordinated tug can they reel in the reward. The chimps know the drill, but Ndyakira can't resist showing Baluku who's boss. She threatens the younger male with a cough and then attacks, chasing Baluku—now screaming—until keepers restore the peace by luring Ndyakira into a neighboring enclosure.

While Ndyakira gets a timeout, Baluku gets a second chance, this time with Okech, a male closer to his age and social rank. The two cooperate like old pros to haul in the banana bounty.

Chimpanzee cooperation depends crucially on individual relationships, says Alicia Melis, a postdoctoral researcher based at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany. Melis has been working with the chimps at the Ngamba Island Chimpanzee Sanctuary since 2004, and she knows her subjects well. Pairs of chimps who get along with each other cooperate readily on the rope-pull task, she has found. But when a pair has a dysfunctional relationship—such as when a dominant chimp like Ndyakira insists on bullying a particular subordinate, or when a lower ranking chimp is too afraid to do its part—cooperation breaks down.

**A tolerant team.** Chimps (*left*) are less able than bonobos (*below*) to cooperate to retrieve a treat of bananas from outside their cage.

CREDITS (TOP TO BOTTOM): G. MILLER/*SCIENCE*; VANESSA WOODS/LOLA YA BONOBO SANCTUARY

"If you can't tolerate each other, you can't work together," says biological anthropologist Brian Hare, Melis's adviser. This idea seems obvious, but Hare thinks it may have important implications for understanding how social skills such as cooperation evolve. He proposes that reduced fear and aggression toward others is a prerequisite for sophisticated social behavior. His recent research on dogs and their relatives support this hypothesis: Foxes bred to be docile around people can also understand some human gestures—a social skill that eludes untamed foxes and that is key to human-canine closeness. Working mainly at sanctuaries such as this one, Hare is now examining how temperament influences social behavior in our two closest living relatives, chimpanzees and bonobos. The results feed into a larger comparative study that is yielding insights into the evolution of human social cognition (see p. 1360).

Other researchers are watching the project with interest. The famously hypersexual bonobos are widely considered the more tolerant of the two apes, says Joan Silk, a primatologist at the University of California, Los Angeles. If bonobos do better at collaborative tasks, when compared head-to-head with chimps, that will support the idea that tolerance is an important precondition for the evolution of social cognition, Silk says: "It will be a great insight if that's correct."

## Ape cooperation

Although chimps cooperate in the wild to attack rival groups and hunt monkeys, until recently, tests of chimp cooperation in more controlled settings have yielded largely negative results. Hare, Melis, and Max Planck Institute collaborator Michael Tomasello wondered whether a lack of "social tolerance"

between the individuals being asked to cooperate might underlie this discrepancy. They carried out their own tests in Leipzig, paying attention to chimp-chimp dynamics. Chimp pairs with high levels of social tolerance, as gauged by their willingness to share food with one another, spontaneously figure out the rope-pull task and consistently work together to get a mutual reward, they reported in the August 2006 issue of *Animal Behaviour*.

The researchers extended those findings with experiments at Ngamba. The tests showed that chimps not only recognize when they need a collaborator to solve a problem, but, given a choice between two potential helpmates, they will also choose the one who has been most effective at helping them in the past (*Science*, 3 March 2006, p. 1297). "Chimps can do really complex things if they're with a tolerant partner, but if they're not with a tolerant partner they can't do anything," says Hare.

There are limits to cooperation even in tolerant chimps, however. When Melis repeats the test with Baluku and Okech but this time rigs the platform with one central bowl of food instead of one bowl for each of them, their collaboration falters. Okech seems to have the right idea: He runs to one end of the rope and stands by, apparently ready to do his part. But Baluku ignores his end of the rope and reaches through the bars of the enclosure, grasping at the fruit just beyond his reach. Another trial produces a similar impasse. On the third try, both chimps pull the rope, but Baluku darts to the food bowl and snatches the fruit, leaving none for Okech, who hoots softly. "He's crying for food," says Melis.

Okech might have had better luck if he'd been a bonobo. Bonobos have a reputation as the free-loving hippie cousins of chimpanzees. They use sex—in a seemingly endless variety of positions and combinations of partners—to defuse the tension of social interactions. Hare hypothesized that these apes, who apparently excel in social tolerance, would outperform chimpanzees in cooperating to retrieve fruit rewards.

That hunch turned out to be right. He, Melis, and colleagues recently had bonobos housed at the Lola Ya Bonobo Sanctuary in the Democratic Republic of Congo perform the rope-pull test. Like many of the chimps, bonobos cooperated readily on the rope-pull task when the reward was separate bowls of fruit. Unlike the chimps, they also cooperated well when the food was presented in a central bowl. Moreover, the bonobo who got

CREDIT: VANESSA WOODS/LOLA YA BONOBO SANCTUARY

## SANCTUARIES AID RESEARCH AND VICE VERSA

It's feeding time at the Ngamba Island Chimpanzee Sanctuary, and keepers are tossing chunks of pineapple, avocado, banana, and papaya to dozens of eager chimps who make a racket as they scramble for the falling fruit. Brian Hare, a biological anthropologist visiting from Germany, looks on gleefully. "Look at all those chimps!" he exclaims. "I love it!"

His work here is part of a project to compare the social behavior of chimpanzees and bonobos (see main text), in particular, cooperation—something at which he himself excels. Although currently based at the Max Planck Institute for Evolutionary Anthropology in Leipzig, it's obvious that he's forged strong relationships here. He exchanges animated greetings with the keepers in Luganda, a local language, and chats with them over dinner about politics—both Ugandan and chimpanzee—catching up on the latest scandals and power struggles in both realms. Hare has also recently established ties with two other African ape sanctuaries and hopes other researchers will follow his lead.

It's a mutually beneficial arrangement, Hare says. Sanctuaries provide a home to animals orphaned by the bush-meat trade or rescued from pet traders, and they promote the conservation of wild apes in the few areas where these animals still remain. They benefit from the support and expertise of visiting scientists. And researchers get their money's worth. Work at the sanctuaries is considerably cheaper and entails less red tape than at many zoos and primate centers, Hare says. Moreover, the sanctuaries have larger numbers of apes than many other facilities and provide more natural living conditions.

At Ngamba, for example, 42 chimpanzees have free rein over 39 hectares of rainforest on the 40-hectare island in the Ugandan section of Lake Victoria. During the day, the chimps forage, play, and interact much like chimps in the wild. They can sleep in the forest too, but most prefer the hammocks slung near the ceiling in the caged enclosure, which doubles as a behavior lab. "It's better for us as researchers because we get to work with apes that are a little more psychologically healthy and have a much richer and [more] natural environment" than zoos or primate centers can provide, Hare says. In addition to work at Ngamba, he has begun studies at the Tchimpounga Chimpanzee Sanctuary in Congo and the Lola Ya Bonobo Sanctuary in the Democratic Republic of Congo, the only sanctuary in the world for these highly endangered apes.

The sanctuaries also stand to gain, says Ngamba director Lilly Ajarova. Hare's research on social relationships among the Ngamba chimps, for example, has taught the keepers a great deal about how different individuals get along and how to manage them, Ajarova says. In addition, Hare's grant money has paid to renovate the sanctuary's kitchen and allowed one of its veterinarians to pursue Ph.D. research in microbiology in Germany.

Harvard primatologist Richard Wrangham, who helped set up the Ngamba sanctuary and encouraged Hare to pursue research there, sees "wins all around, for chimpanzees, managers, and researchers." Like Hare, he would like to see the sanctuaries become a sharable resource for ape researchers, whose populations of subjects in developed countries may dwindle as breeding restrictions tighten (*Science*, 1 June, p. 1265). "The sanctuaries are a godsend for the future of our science," Hare says. **–G.M.**

to the prize first always shared some food with its partner. (Like Baluku, most chimps adopt a winner-take-all policy in this situation.) The findings, which appeared in the 3 April issue of *Current Biology*, suggest to Hare that relative to chimps, bonobos are capable of more flexible cooperation: They are less fussy about who they will work with or what the reward is.

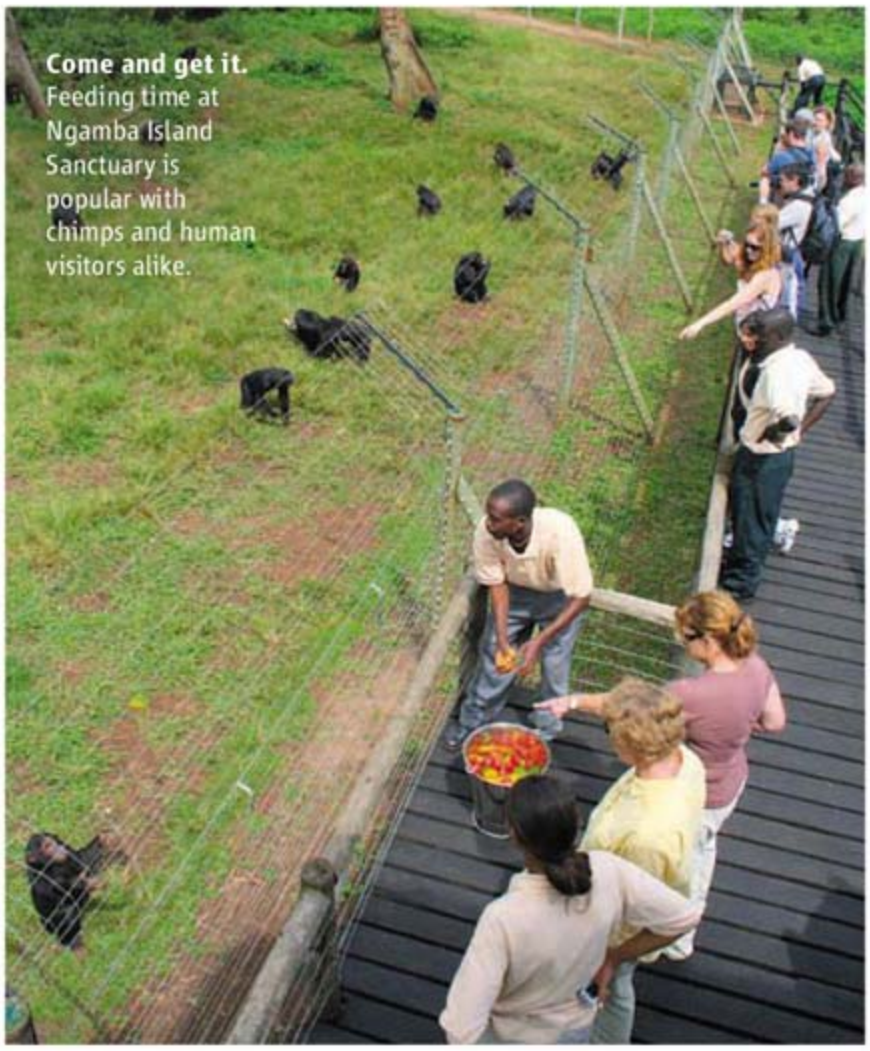
Still, the study presents a puzzle because field researchers have seen very little cooperation in wild bonobos. One possibility, Hare says, is that bonobos don't need to cooperate because food is so abundant in their rich rainforest habitat. Tomasello adds that although bonobos, unlike chimps, don't appear to use tools in the wild, they quickly learn to use them in captivity, suggesting they're capable of a variety of cognitive feats they don't normally perform in the wild.

**Thought provoking.** Comparative behavioral studies of nonhuman primates such as bonobos (*above*) should shed light on the roots of human social cognition.

### Evolution of tolerance

But how did bonobos get to be so socially adept? Hare has a provocative idea, one suggested by work in canines. Domestication has honed the dog's social smarts. Dogs know when a human is pointing toward hidden food, implying complex communication between man and his best friend. Wolves and wild foxes lack this ability. But foxes bred to lack fear or aggression toward humans can interpret these gestures just fine, Hare and his colleagues reported in 2005. "They weren't selected to do anything cognitively sophisticated," says Tomasello. Yet domestication produced social skills that wild ancestors lacked (*Science*, 23 June 2006, p. 1737).

Hare's Ph.D. adviser at Harvard, primatologist Richard Wrangham, had proposed in the 1990s that something analogous may have happened in bonobos after their lineage split off from that of chimpanzees about 2 million years ago. Dogs and other domesticated animals tend to have certain characteristics relative to their wild ancestors, including reduced cranial volume, smaller teeth, more gracile limbs, and lighter coloring. Wrangham argued that bonobos, and the males in particular, have these traits relative to chimpanzees. These features arose coincidentally in dogs and domestic foxes selectively bred for low aggression, and Wrangham argues that natural selection against aggression in bonobos could have produced a similar result. Bonobos are the most peaceful of the great apes, he says. Male bonobos don't conduct raids on neighboring groups, as do chimpanzees, for example, or kill infants sired by other males, as do gorillas. (Why natural selection would have disfavored aggression in bonobos is a mystery, although Wrangham is not short on ideas.)



**Come and get it.** Feeding time at Ngamba Island Sanctuary is popular with chimps and human visitors alike.

Hare goes a step further, proposing that, whatever the cause, selection against aggression enhanced social tolerance in bonobos, setting the stage for their ability to cooperate more flexibly than chimpanzees in some situations. "It's a racy hypothesis," Hare concedes. "It's not going to be embraced by everyone."

Primatologist Frans de Waal of Emory University in Atlanta, Georgia, is one of the unconvinced. He discounts Wrangham's assertion that bonobos arose from a chimplike common ancestor that became less aggressive after they diverged. "It could very well be the other way around," he says. Chimpanzees could be the more aggressive offshoot of a bonobolike ancestor. "There's not a shred of evidence for one position or the other at this point," de Waal says, adding that only genetic data are likely to settle the issue.

Researchers have done very little genetic work with bonobos to date. But one study that compared variations in a gene called *avpr1a* in bonobos and chimpanzees found that the bonobo version is similar to one found in highly social prairie voles, whereas the chimp version resembles that found in socially aloof montane voles (*Science*, 10 June 2005, p. 1630). The human version is more similar to the bonobo one. The gene encodes a receptor for vasopressin, a hormone linked to aggression, sex, and other social behaviors. The findings hint at how genetic changes could produce different temperaments in chimps and bonobos, Hare says.

Hare is currently searching for additional clues by measuring heart rate and other physiological indicators in bonobos and chimps in response to social stimuli such as the recorded calls of familiar and unfamiliar individuals. "If we can figure out how those two sister species are different and how they became different, then we'll be able to make strong inferences about how we became different from them," he says. "That's the goal of the whole project."

–GREG MILLER

CREDITS (TOP TO BOTTOM): VANESSA WOODS/LOLA YA BONOBO SANCTUARY; G. MILLER/*SCIENCE*

NEWS

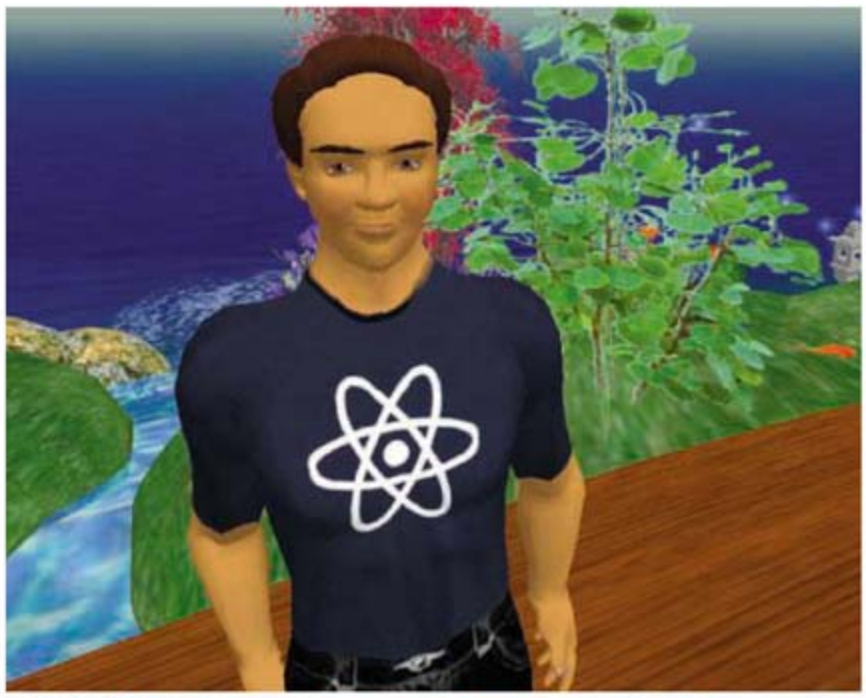
# The Promise of Parallel Universes

For social psychologists, computer-generated realities provide exciting new terrain for exploring human behavior and complex social interactions

In Second Life, there's no need for liposuction. Participants in this computer-generated world can slim down by simply sliding a bar on the computer screen that controls the body fat of their virtual self, or avatar. Receding hair fills out with similar ease and, if the whim strikes, turns electric blue with a click of the mouse.

The freedom to try out different looks, and even different personas, contributes to the growing appeal of virtual worlds such as Second Life, where residents socialize in real time, often forming groups to pursue business, artistic, and other endeavors. These parallel universes have attracted millions of users in recent years. They've also begun to attract the attention of scholars of human social behavior.

For researchers, virtual worlds are uncharted territory, test beds for seeing what people do when freed from real-world physical and social constraints. "It's a deep, deep rabbit hole," says Dmitri Williams, who studies the social impact of new media at the University of Illinois, Urbana-Champaign. Social scientists are investigating whether social norms, such as the concept of personal space, persist in these modern-day Wonderlands. They're also looking into whether, by creating better-than-life avatars, virtual-world visitors set themselves up to have different online identities: For example, can a tall, handsome avatar transform a shy nerd into a smooth operator? In turn, can experiences in the virtual realm change how people behave and think of themselves in real life?



**Instant makeover.** The malleability of avatars adds a new dimension to social interactions in virtual environments.

CREDITS (TOP TO BOTTOM): COLLABORATIVE WORK OF N. KEVITIYAGALA/*SCIENCE*, ALISON CHANDLER, G. MILLER/*SCIENCE*

Already, they are seeing signs that computer-generated representations of people can be deviously manipulative, with the potential to impact real-world decisions (see sidebar, p. 1343). Thus, answering these questions will be of fundamental importance as virtual environments increasingly enter the mainstream, says Williams. "It's possible that one large category of human interactions in the future is going to be based on avatars," he adds.

At the same time, some researchers see opportunities to tackle previously intractable research questions. They can do experiments in virtual environments on social networks and crowd behavior, for example, that would otherwise be impossible for practical or ethical reasons. "This is a very exciting way forward for social psychology and sociology," says Mel Slater, a computer scientist with joint appointments at University College London and the Universitat Politècnica de Catalunya in Barcelona, Spain.

## Science in wonderland

Science-fiction authors have written about virtual worlds for decades, but only in recent years have more powerful computers and widespread broadband Internet access made it possible for people to interact in real time in computer-generated settings. Virtual environments vary in content and character. Some are games with set rules. The most popular of this genre is World of Warcraft, in which, simultaneously, thousands of players battle monsters and enemy players, accumulating points and booty and risking their avatars' lives in the process. In contrast, Second Life is a safer but more freeform world, with few limits on situations encountered.

Yet even in virtual worlds, the mind follows some real-world rules. "In a lot of these online games, it's possible to actually walk through another character, but almost no one ever does that because it's so uncomfortable psychologically," explains Nick Yee, who recently completed a Ph.D. at Stanford University in Palo Alto, California, on the psychology of online games and virtual environments. Indeed, Yee and others have found that people maintain a certain distance when interacting with other avatars. Just as in the physical world, pairs of female avatars in Second Life made more eye contact while talking and tended to stand closer together than did pairs of males, Yee and colleagues, including his graduate adviser Jeremy Bailenson, reported in the February issue of *CyberPsychology & Behavior*. Avatars also tended to reduce eye contact as the distance between them shrunk,

**Brave new worlds.** Social scientists are finding that virtual environments provide prime opportunities to study group behavior.

the researchers found. "There are some things that are so hard-wired culturally that it's hard to switch them off, even in a virtual environment," Yee says.

In another study, now in press at the *International Journal of Multimedia Tools and Applications*, Yee and Bailenson asked student volunteers to clean "dirt spots" off several virtual objects and people using a joystick that measures the force applied by the user's hand. The subjects applied more force when wiping the dirt from the objects than from the people, Yee and Bailenson found. Volunteers also applied a softer touch to faces relative to torsos and to females relative to males, mirroring real-world tendencies regarding touch.

On the other hand, virtual worlds offer visitors a chance to break away from their normal habits. In a paper in press at *Human Communication Research*, Bailenson and Yee report that undergraduate volunteers given an attractive avatar more readily approached and conversed with an avatar of the opposite sex than did volunteers given a less attractive avatar. In another experiment, they found that volunteers given a taller avatar negotiated more confidently when they had to split money with another avatar and were less likely to accept a lopsided deal than were volunteers given a shorter avatar. "How your avatar appears affects how you behave online," says Yee. Moreover, he has found that those given taller avatars gained confidence in a subsequent face-to-face negotiation task in real life.

Other researchers have also seen evidence of a carryover from the virtual world to the physical one. Psychologist Jeffrey Hancock and his graduate student Jorge Peña at Cornell University recently asked volunteers to explore a virtual environment as an avatar wearing a doctor's coat or one wearing the white robe and hood of the Ku Klux Klan. Afterward, a personality test revealed that those dressed as a member of the white-supremacist group rated themselves more aggressive than did the virtual M.D.'s, who gave themselves high marks for friendliness. The difference in the responses of the two groups was too large to be explained by chance differences in the personalities of the people assigned to the two groups. Hancock says: "These questionnaires are supposed to examine stable traits about somebody that aren't supposed to change over time. Yet here we're seeing that they're actually thinking about themselves differently" after a brief experience in a virtual environment.

## Group dynamics

Whereas researchers such as Bailenson and Hancock have focused primarily on individual behavior, others see unprecedented opportunities to investigate the behavior of larger groups. "Virtual worlds provide an outstanding exploratorium for us to gather data and test models," says Noshir Contractor, who studies social networks at Northwestern University in Evanston, Illinois.

In the real world, collecting data on how people create, maintain, and dissolve links with one another is incredibly labor- and time-intensive, Contractor says. For example, beginning in 1999, he spent $1.5 million and 3 years on a project that examined how groups of people access the expertise of their members when they work collaboratively on a problem. Companies and organizations often assume that if they create a directory listing the expertise of their members, people will seek out the most knowledgeable person when they need help with a particular aspect of a job. To see if that was really happening, he and his colleagues conducted in-depth surveys with more than 30 working groups at places such as NASA, Boeing, and Charles Schwab. "Getting the data for that was very time-consuming and very painstaking," Contractor recalls. His team found that when people need help with a particular aspect of a job, they don't necessarily go to the person with the most expertise in that area; instead, they often get help from people with whom they have close social ties.

More recently, Contractor and co-workers conducted a similar experiment in World of Warcraft. This time around, the experiment took only a few months, and the findings turned out much the same: Even though the game provides lists of players best able to craft deadly weapons or construct defenses, when players needed help, they typically turned instead to other players they already knew or had worked with in the past.

Contractor is now extending this line of investigation with studies on social networks in EverQuest II, a monster-slaying game produced by Sony, and in Second Life, which will enable him to study thousands of individuals instead of just a few dozen, as in his real-world study. Contractor hopes these more comprehensive data sets will shed light on how social networks change over time, something that has been very difficult to track. In the case of EverQuest, Sony has granted the researchers access to 15 months of in-world action archived second by second as players form and dissolve groups for quests and raids. "We essentially have a movie of the networks as they're unfolding in time," says Contractor.

**Shocking.** A virtual woman receives increasingly painful shocks in a 21st century version of Stanley Milgram's infamous obedience experiment.

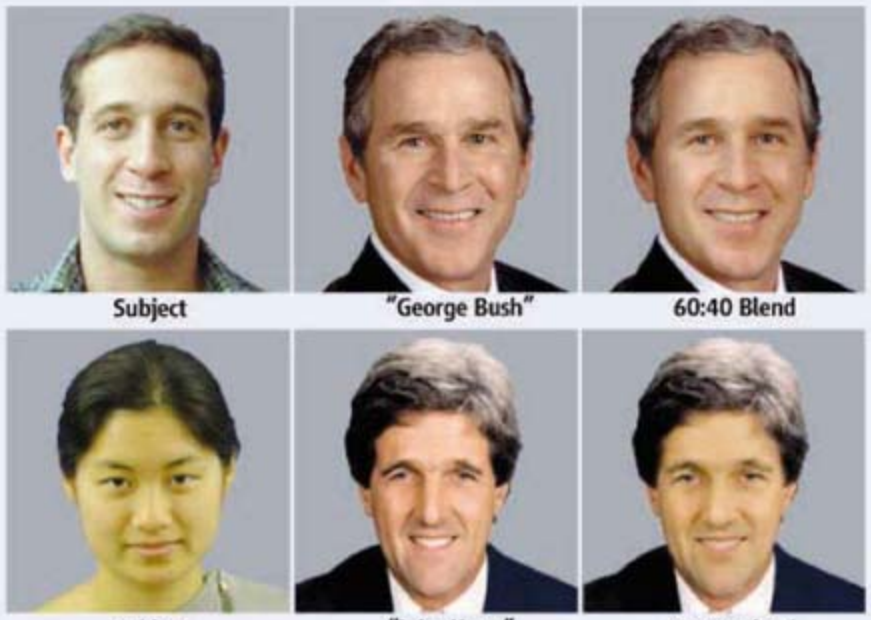
CREDITS (TOP TO BOTTOM): WALTER J. JONES; MEL SLATER

## THE ART OF VIRTUAL PERSUASION

If virtual worlds go the way of the World Wide Web, eventually hundreds of millions of people will be logging in daily for a spin around their favorite computer-generated world. But they will have to keep their wits about them. Social scientists are finding that online experiences influence offline thinking (see main text) and that manipulation—for political, advertising, or other purposes—may be much more sophisticated in virtual environments.

A variety of studies have shown that people who mimic the gestures or speech of others are often perceived by those they mimic as more likable and influential. In virtual environments, where everything is generated by computers, the potential for manipulation by mimicry can reach frightening new levels.

For example, a week before the 2004 U.S. presidential election, Jeremy Bailenson and colleagues at Stanford University asked 240 volunteers to fill out surveys regarding the two main candidates, President George W. Bush and Senator John Kerry, while viewing side-by-side photographs of the two men. For a randomly selected third of the subjects, the researchers used software to merge Bush's photo with a photo of the subject, making Bush look more like the subject without the subject noticing. Another third faced a Kerry doctored with their features, and for the remainder, the photos were unaltered. After viewing the photos, those subjects without strong partisan views tended to endorse the candidate whose face had been morphed with their own.




**How do you like me now?** Undecided voters gravitate toward a candidate whose face has been morphed with their own.

CREDIT: JEREMY BAILENSON

In another experiment, in 2005, Bailenson and colleagues asked undergraduate volunteers to don a virtual-reality helmet to watch someone argue for an unpopular real-life proposal that students carry an ID card at all times. When the virtual talking head mimicked the viewer's own head movements (as recorded and relayed by the helmet), the student responded more favorably to questions about the policy.

Such findings have potentially creepy implications. "It gets kind of icky if you think about politicians in the future that will change what they look like according to who's looking at them," says Jeffrey Hancock, a psychologist at Cornell University. Of course, politicians already do that to some extent in the real world—donning overalls for a meeting with farmers, then switching to a suit for a meeting with business executives—but in virtual environments, computer algorithms could potentially enable a politician's (or a salesperson's) avatar to adjust his appearance and mannerisms instantly and automatically to maximize his influence in any given situation. In Second Life and other virtual environments, Bailenson points out, computer servers keep a running log of everything—every glance, nod, or flick of the hand that happens. "You have this huge database, and someone could grab it in real time and mimic you at a subtle level," he says. "I think it's important for people to realize how difficult it is to detect this when it happens in the digital world and how powerful it is."

At the same time, Bailenson says, the power of mimicry could have beneficial uses as well—to create avatars for teachers that are personalized for each student, for example. "If I'm a teacher and I really want to reach a student, I have a new tool," he says. **–G.M.**

Other researchers have begun toying with virtual worlds as settings for experiments that could not pass muster with ethical review boards if done with real people, yet which have the potential to provide valuable insights into human behavior. Slater recently explored this potential by conducting a virtual version of a controversial 1960s experiment designed by psychologist Stanley Milgram at Yale University. Milgram and colleagues directed subjects to deliver increasingly painful electric shocks to a stranger (really an actor pretending to be in pain) when he gave an incorrect response on a memory test. The subjects' compliance pointed to a disturbing tendency to obey authority.

In Slater's version, the stranger was a virtual woman viewed on a computer screen. Although subjects knew the woman was not real, their heart rates increased and they reported feeling bad about delivering the shocks. Yet they kept shocking the stranger just as Milgram's subjects had, Slater and colleagues reported in the December 2006 issue of *PLoS ONE*. The experiment is an important proof of principle, Slater says, because it suggests that virtual environments can be used to predict how people will behave in real situations.

Slater now plans to investigate how crowds behave in emergencies. For example, social psychologists have struggled to explain the so-called bystander effect, whereby people are less likely to help someone who is being attacked when there are others present. "There are various hypotheses out there, but they can't be tested" in real life, Slater says. In a virtual environment, however, he can easily control the number and behavior of people in any given situation. He also plans to examine how the behavior of a crowd at a virtual movie theater influences how individuals respond when a fire breaks out. "The beauty of virtual reality is that it allows you to study these quite complex issues while sidestepping the practical and ethical problems inherent to real-world versions of such experiments," Slater says.

Researchers such as Contractor and Slater hope their work will ultimately lead to practical applications, from better disaster management to increased collaboration and creativity within organizations. Indeed, some blue-chip companies are already taking note. In June, IBM released a study of online role-playing games that concluded that these virtual environments provide fertile ground for developing real-world leadership skills. In a not-so-far-fetched future, applicants for management positions may find themselves listing their World of Warcraft credentials on their résumés right under their university business degrees.

**–GREG MILLER**

REVIEW

# Evolution in the Social Brain

R. I. M. Dunbar* and Susanne Shultz

The evolution of unusually large brains in some groups of animals, notably primates, has long been a puzzle. Although early explanations tended to emphasize the brain's role in sensory or technical competence (foraging skills, innovations, and way-finding), the balance of evidence now clearly favors the suggestion that it was the computational demands of living in large, complex societies that selected for large brains. However, recent analyses suggest that it may have been the particular demands of the more intense forms of pairbonding that was the critical factor that triggered this evolutionary development. This may explain why primate sociality seems to be so different from that found in most other birds and mammals: Primate sociality is based on bonded relationships of a kind that are found only in pairbonds in other taxa.

The brain is one of the most expensive organs in the body, second only to the heart: The brain's running costs are about 8 to 10 times as high, per unit mass, as those of skeletal muscle (*1*, *2*). Although the brain's ability to control the body's functions is obviously useful, it entails something of an evolutionary puzzle. The neurobiologist Harry Jerison first pointed this out during the 1970s (*3*), when he drew a distinction between the component of the brain required to meet the body's physical needs and the component that was left over, which could attend to tasks of a more cognitively complex nature. This second component of the brain has been increasing over evolutionary time across the birds and mammals, but fish and reptiles continue to thrive with brains of very modest size. Although it is easy to understand why brains in general have evolved, it is not so obvious why the brains of birds and mammals have grown substantially larger than the minimum size required to stay alive.

Traditional explanations for the evolution of large brains in primates focused either on ecological problem solving or on developmental constraints. Early studies identified physiological and life-history traits—including large body size, metabolic rates, and prolonged development—that were associated with large brains (*4*, *5*). Some argued that this correlation was due to the more efficient metabolism of larger-bodied animals, which allowed more energy to be devoted to fetal brain growth and thereby made the evolution of larger brains possible (*6*, *7*). All else being equal, big brains are a useful if unintended by-product of efficient energy use. In addition to this theory, some evidence supported ecological problem-solving as a possible explanation: Among primates, large-brained species have larger home ranges (perhaps requiring more sophisticated mental maps), and frugivores have larger brains than folivores (fruits are much less predictable in their location and availability than leaves) (*8*).

On closer examination, most of the energetic explanations that have been offered identify constraints on brain evolution rather than selection pressures. In biology, constraints are inevitable, and crucial for understanding evolutionary trajectories, but they do not constitute functional explanations—that is, just because a species can afford to evolve a larger brain does not mean that it must do so. Proponents of developmental explanations seem to have forgotten that evolutionary processes involve costs as well as benefits. Because evolution is an economical process and does not often produce needless organs or capacities, especially if they are expensive to maintain, it follows that some proportionately beneficial advantage must have driven brain evolution against the steep selection gradient created by the high costs of brain tissue. In this respect, most of the ecological hypotheses proposed to date also fail. None can explain why primates (which have especially large brains for body mass, even by mammal standards) need brains that are so much larger than, say, squirrels, to cope with what are essentially the same foraging decisions.

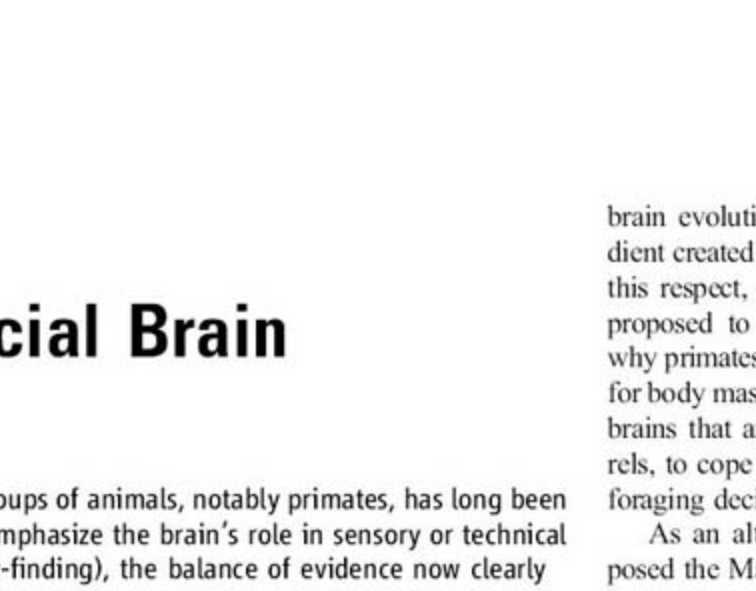



**Fig. 1.** In anthropoid primates, mean social group size increases with relative neocortex volume (indexed as the ratio of neocortex volume to the volume of the rest of the brain). Solid circles, monkeys; open circles, apes. Regression lines are reduced major axis fits. [Redrawn from (*47*)]

As an alternative, Byrne and Whiten proposed the Machiavellian Intelligence hypothesis (*9*) in the late 1980s: They argued that what differentiates primates from all other species (and, hence, what might account for their especially large brains) was the complexity of their social lives. Unfortunately, the term "Machiavellian" was widely interpreted as implying deceit, manipulation, and connivance—traits that most people were reluctant to attribute to any species other than humans. In fact, although these are potential aspects of social complexity, they did not lie at the heart of Byrne and Whiten's proposal. Instead, the proposal emphasized the complex social environments in which primates lived. The less contentious label social brain hypothesis (SBH) (*10*, *11*) has thus been adopted.

Although initially criticized for being conceptually vague, the SBH eventually began to receive increasing quantitative support. A series of studies demonstrated that, among primates at least, relative brain size [usually indexed as relative size of the neocortex, the area that has disproportionately expanded in primates (*12*)] correlates with many indices of social complexity, including social group size (Fig. 1) (*13*), number of females in the group (*14*), grooming clique size (*15*), the frequency of coalitions (*16*), male mating strategies (*17*), the prevalence of social play (*18*), the frequency of tactical deception (*19*), and the frequency of social learning (*20*).

A weakness of most analyses, however, is that they invariably test a single hypothesis without ensuring that the same predictions could not also arise from other equally plausible explanations. Although some attempts have been made to discriminate between ecological and social theories (*13*, *21*), and these have largely supported the social hypothesis, there has been little effort to develop an explanatory framework that integrates the many social, ecological, and life-history correlates of brain size that have been identified. As a result, constraint-type explanations (e.g., correlations with life history)

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have continued to be emphasized as though they were alternative explanations for evolutionary function.

### Social Brain, Social Complexity

The broad interpretation of the social brain hypothesis is that individuals living in stable social groups face cognitive demands that individuals living alone (or in unstable aggregations) do not. To maintain group cohesion, individuals must be able to meet their own requirements, as well as coordinate their behavior with other individuals in the group. They must also be able to defuse the direct and indirect conflicts that are generated by foraging in the same space.

Appreciating that the problem to be solved lies at the level of the group (i.e., the need to maintain group coherence through time) and not just at the level of individual foraging strategies might allow us to reconcile the apparent conflict between the ecological and social hypotheses. One example of this apparent conflict is the suggestion that flexibility of foraging skills might be more important than social skills. The evidence that brain size correlates with technical innovation and the acquisition of new food sources through social learning (or cultural transmission) in both birds (*22*) and primates (*20*) supports this claim. However, in the final analysis, all of these hypotheses (social and ecological alike) are at root ecological: They allow animals to survive and reproduce more effectively. The SBH proposes that ecological problems are solved socially and that the need for mechanisms that enhance social cohesion drives brain size evolution. In contrast, the more conventional ecological hypotheses assume that animals solve these same ecological problems individually by trial and error learning and do not rely on any form of social advantage.

For primates at least, sociality is specifically driven by the need to minimize predation risk (*23*–*25*). However, we have shown that two different kinds of predators (chimpanzees and felids) from five different ecological communities on two continents differentially select small-brained prey species (relative to their availability in the population) when we control for other traits (including group size) (*26*). Predation thus acts directly and indirectly (by means of group size) on brain evolution. Nonetheless, whatever its advantages, group living incurs substantial costs, both in terms of ecological competition and, for females, reproductive suppression (*23*, *24*). Hence, behavioral flexibility within a social situation may be essential for individuals to make the most of sociality. For anthropoid primates, this behavioral flexibility is in part reflected in the use of intense social bonds (often, but not always, serviced by social grooming) to prevent groups from disintegrating under these pressures (*15*).

The net consequence of these kinds of pressures is that species that evolve larger brains ultimately have higher fitness. Jerison (*3*) himself pointed out that, in the Paleolithic record, increases in brain size among carnivores and their prey species (mainly ungulates) seem to track each other closely over time, with ungulate brain size leading. These findings are interesting in themselves and also mesh well with findings that brain size can be associated with other types of ecological flexibility—for example, that brain size is a predictor of both extinction risk and invasion success in birds (*27*, *28*).

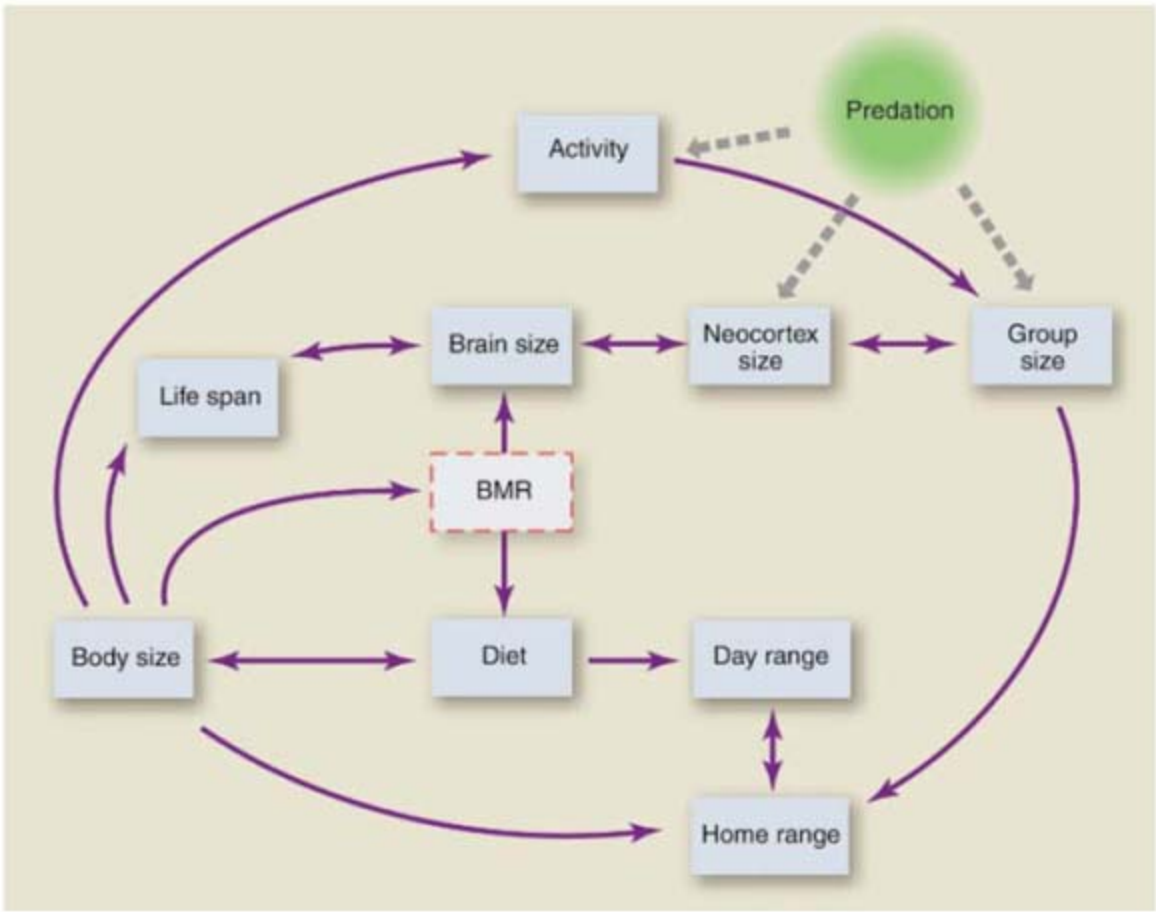


**Fig. 2.** Path analysis of correlates of brain size in primates. The best model for group size included just three variables (neocortex size, activity, and range size). Factors that are more remote in the path diagram provide a significantly poorer fit, suggesting that they act as constraints rather than driving variables. BMR, basal metabolic rate. [Reproduced with permission from (*16*)]

To tease out the relationship between the nexus of factors that correlate with brain size, we have recently undertaken path analyses of primate and bird data to identify causes, consequences, and constraints in brain evolution (*16*). These analyses demonstrate not only that energetics (i.e., ecology) and life history impose constraints on brain size (such that these constraints require solutions if a species is to evolve a substantially larger brain) but also that the key selection pressure promoting the evolution of large brains is explicitly social (Fig. 2).

### Brain Evolution in Birds and Mammals

Although the SBH was originally conceived for primates, the same principle could apply more widely, and several attempts have been made to extend the hypothesis to nonprimate taxa, including ungulates (*29*, *30*), carnivores (*31*), bats (*32*), and even birds (*33*), albeit with somewhat mixed results. Indeed, several studies have argued that sexual selection rather than sociality might be a more important factor driving brain evolution (*32*, *34*). Yet evidence shows that the correlation is the reverse of what one might expect (polygamous species actually have the smallest brains), making sexual selection an unlikely suggestion, although it may influence some components of the brain [such as the limbic system in male primates (*35*, *36*)].

Although it is possible that the SBH applies exclusively to primates, biologists are usually reluctant to argue for special cases. Fortunately, the recent availability of more powerful statistical tools has allowed us to resolve this enigma. First, we have shown that there is a strong coevolutionary relationship between relative brain size and the evolution of sociality from an asocial (or less social) state in primates, ungulates, and carnivores (*31*). Second, for four orders of mammals (primates, bats, artiodactyl ungulates, and carnivores) and 135 species of birds representing a wide cross-section of avian orders, we have shown that, in all taxa except anthropoid primates, the relationship between brain size and sociality is qualitative and not

quantitative: In each case, large relative brain size is associated explicitly with pairbonded (i.e., social) monogamy (Fig. 3).

These findings suggest that it may have been the cognitive demands of pairbonding that triggered the initial evolution of large brains across the vertebrates. More important, pairbonding is the issue, not biparental care. This is obvious in the case of ungulates: Biparental care does not occur at all in this taxon, yet ungulates that mate monogamously have substantially larger brains than those that mate polygamously (Fig. 3).

### How Complex Can Pairbonds Be?

The important issue in the present context is the marked contrast between anthropoid primates and all other mammalian and avian taxa (including, incidentally, prosimian primates): Only anthropoid primates exhibit a correlation between social group size and relative brain (or neocortex) size. This quantitative relationship is extremely robust; no matter how we analyze the data (with or without phylogenetic correction, using raw volumes, or residuals or ratios against any number of alternative body or brain baselines) or which brain data set we use (histological or magnetic resonance imaging derived, for whole brain, neocortex, or just the frontal lobes), the same quantitative relationship always emerges. This suggests that, at some early point in their evolutionary history, anthropoid primates used the kinds of cognitive skills used for pairbonded relationships by vertebrates to create relationships between individuals who are not reproductive partners. In other words, in primates, individuals of the same sex as well as members of the opposite sex could form just as intense and focused a relationship as do reproductive mates in nonprimates. Given that the number of possible relationships is limited only by the number of animals in the group, primates naturally exhibit a positive correlation between group size and brain size. This would explain why, as primatologists have argued for decades, the nature of primate sociality seems to be qualitatively different from that found in most other mammals and birds. The reason is that the everyday relationships of anthropoid primates involve a form of "bondedness" that is only found elsewhere in reproductive pairbonds.

This suggestion merely adds to the puzzle of social bonding. What is it about social bonds that is cognitively so demanding? There seem to be two obvious possibilities in the case of reproductive pairbonds. One is that lifelong monogamy is a risky commitment; to avoid the risk of bearing a disproportionate share of the costs of reproduction, individuals must be especially careful in choosing good-quality (i.e., fertile) mates who will be reproductively loyal and play their full role in the processes of rearing. The other possibility is that a working reproductive relationship that involves substantial postnatal parental investment requires very close coordination and behavioral synchrony; if successful rearing requires both partners to invest time and energy in the rearing process, then the pair needs to regulate its activities so that each has enough time for feeding and rest. That will usually necessitate some degree of activity synchronization—in some cases, to ensure the pair do not drift apart as a result of different activity schedules, and in other cases, to ensure that rearing or vigilance duties are time-shared appropriately (*37*). Which of these two has been the key driver for brain evolution, or whether both have been equally important, remains to be determined.

It has become apparent that we lack adequate language with which to describe relationships, yet bondedness is precisely what primate sociality is all about. Intuitively, we know what we mean by bondedness because we experience it ourselves, and we recognize it when it happens. The problem, perhaps, is that bondedness is an explicitly emotional experience and language is a notoriously poor medium for describing our inner, emotional experiences. Because relationships do not have a natural objective cognitive dimension that we can easily express in language, comparing the bondedness of different species is difficult (this may also explain why ethologists have invariably ducked the problem completely, preferring observable descriptions of behavior to grappling with what is going on inside the animal).

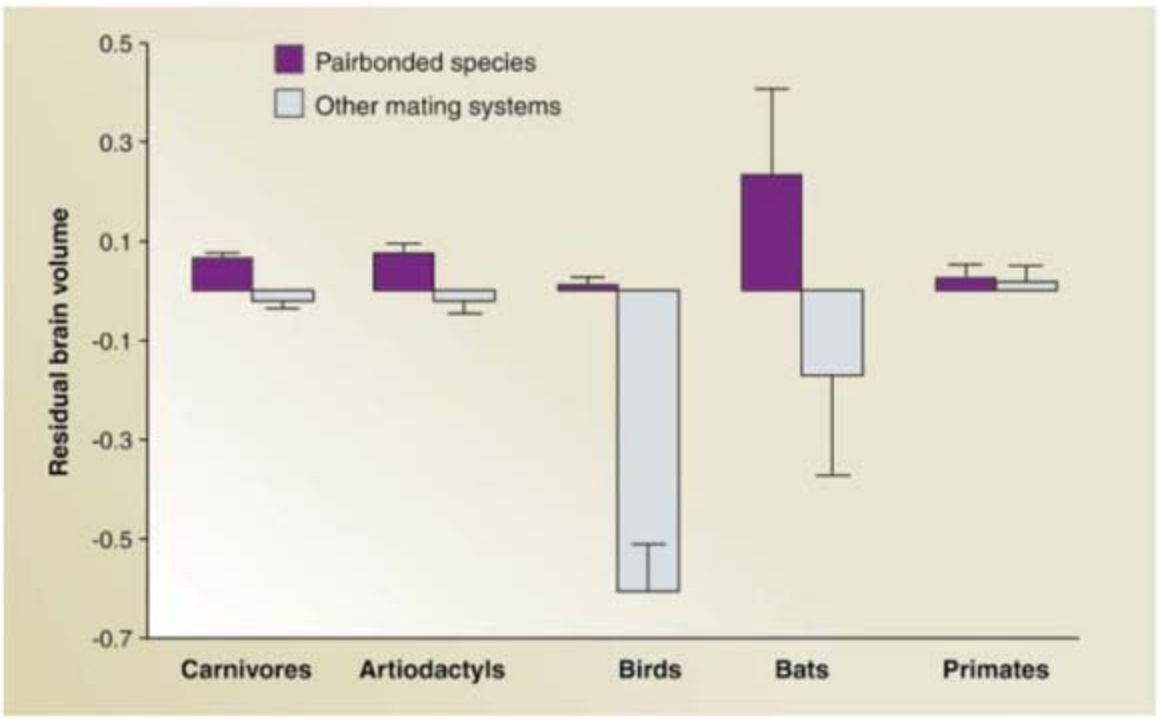


**Fig. 3.** Mean (±SE) of residual brain volume (controlling for body size and phylogeny) in species with pairbonded (purple bars) versus all other mating systems (gray bars) in birds and four orders of mammals. The differences are significant in all cases except primates.

Part of the problem here is that social relationships have been seen as mere epiphenomena spawned by the issues of real biological interest, namely mate choice and parental investment. The social learning version of SBH (*20*, *22*) inherits a sense of that assessment: Sociality is of interest only in so far as it provides a context in which animals can acquire foraging information that has immediate benefits for them in terms of individual fitness. However, this misses the point of primate sociality—indeed, the nature of sociality, and especially pairbonding—in all higher vertebrates. In these intensely social species, social relationships are not so much an emergent property of mating and parenting strategies as the means to achieving those strategies. A group of this kind is an implicit social contract: To form a group that provides a benefit of cooperation (for example, reducing predation risk), members are necessarily obliged to trade off short-term losses in immediate benefits in the expectation of greater gains in the long term through cooperation. Fitness payoffs are determined not by an individual's immediate "here-and-now" personal fitness, but by the extent to which the group can generate longer-term payoffs for the individual. In effect, we are dealing explicitly with multilevel selection and the long-overlooked topic of niche construction (*38*). Once we understand this, the reasons why animals should invest in relationships become clear. Relationships provide the key to fitness benefits at the group level, and the "trickle-down" benefits are reaped by the individual (*39*). An individual will be prepared to invest in social strategies that create groups if, by doing so, it gains higher net

fitness (i.e., at the end of its lifetime) than pursuing more individualistic strategies.

### What Microneurobiology Has to Tell Us

There has, of course, been growing interest in recent years in some of the neurobiological correlates of social bonding. Particular interest has focused the role of oxytocin (and its male equivalent, vasopressin) in pairbonded species (*40*), but other neuropeptides have also been identified as playing an important role in social bonding [e.g., endorphins (*41*)]. In addition, a parallel interest has been developing in the role of several specific neuronal assemblages, including mirror neurons (*42*) and so-called spindle cells in the anterior cingulate cortex (*43*), as well as in specific genes such as GLUD2 [a retrogene, derived from glutamate dehydrogenase, which is responsible for clearing the by-products of neuron activity (*44*)] and the abnormal spindle-like microcephaly-associated (ASPM) gene and microcephalin, which are implicated in brain growth (*45*).

Each of these has been seen by their respective protagonists as the holy grail for understanding both social cognition generally, and, in particular, for explaining the differences between humans, apes, and monkeys (*43*, *46*). There is no question that these are individually important and novel discoveries, and they undoubtedly all play a role in the nature of sociality. However, there is a great deal more to how and why humans are different from other apes, or why apes are different from monkeys. We will need better studies of cognition and behavior to answer these questions. More important, perhaps, is one key point: Species differences in a handful of very small neuronal components do not explain the apparent need for massive species differences in total brain size. Most of these studies fall into the same trap as the developmental explanations for brain size did in the 1980s: They mistake mechanistic constraints for evolutionary function. It is unclear why this point continues to be ignored, but we will still have a lot of explaining to do about volumetric differences in brains.

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REVIEW

# Social Components of Fitness in Primate Groups

**Joan B. Silk**

There is much interest in the evolutionary forces that favored the evolution of large brains in the primate order. The social brain hypothesis posits that selection has favored larger brains and more complex cognitive capacities as a means to cope with the challenges of social life. The hypothesis is supported by evidence that shows that group size is linked to various measures of brain size. But it has not been clear how cognitive complexity confers fitness advantages on individuals. Research in the field and laboratory shows that sophisticated social cognition underlies social behavior in primate groups. Moreover, a growing body of evidence suggests that the quality of social relationships has measurable fitness consequences for individuals.

Life in primate groups rivals the best television soap opera—the weak are often exploited by the powerful; strong alliances and lasting bonds are formed; dynasties are established, but are occasionally toppled; and not all of your favorite characters survive the season. Ecological constraints generate the dramatic tension, and natural selection crafts the plot. The complicated storylines reflect the fact that primates have evolved large brains, sophisticated social cognition, and complex social relationships (Fig. 1). There has been considerable discussion of the selective pressures that favor the evolution of large brains in social species (*1*–*4*), but it has has not been clear how large brains, social cognition, and social relationships are translated into fitness advantages for individuals. New evidence indicates that the competitive success and reproductive performance of individuals in primate groups is affected by the nature and quality of the relationships that they form. These data enable us to tie together what we have learned from comparative analyses of brain morphology, experimental studies of social cognition, and naturalistic observations of the structure of social relationships in primate groups.

### What the Social Brain Knows

The capacity to develop complex social relationships may be an important benefit derived from having a "social brain." According to the social

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intelligence hypothesis, the challenges of living in social groups have favored the expansion and reorganization of the primate brain (*1*, *2*). The hypothesis is supported by comparative analyses that show that various measures of brain size are positively related to the size of social groups in primates and other taxa. But if it were only the size of social groups that mattered, wildebeest would be wizards. Instead, small-brained wildebeest graze the plains in largely anonymous unstructured herds. The primate's social brain is specially designed to enable individuals to manage social relationships. Thus, brain size is also connected to what goes on within social groups and is correlated with the size of grooming networks that primates form and the frequency of coalitions, social play, tactical deception, innovation, and social learning (*2*).

Primates are endowed with cognitive abilities that are especially well suited to tracking social information. For example, primates are able to recognize individuals; identify kin; compute the value of resources and services; keep track of past interactions with group members; make transitive inferences; discriminate between cooperators and defectors; and assess the qualities of prospective rivals, mates, and allies (*3*–*5*).

Primates also know something about the nature of relationships between other group members (*3*–*5*). The first evidence that primates know something about the relationships of others, which is sometimes called third-party knowledge, came from playback experiments conducted on wild vervet monkeys (*Cercopithecus aethiops*) (*6*). When females heard the screams of their own offspring played from a speaker hidden in the brush, they peered intently into the bushes. Other females sitting nearby did not look for the distressed juvenile, they looked at the mother. Their reactions indicated that they recognized the identity of the caller, and they were able to match the caller to its mother. Similarly, when monkeys are threatened by other group members, they are more likely to redirect aggression toward a relative of a former opponent than toward a random group member (*7*–*10*), and they are more likely to reconcile conflicts with close kin of their former opponents than with individuals who are unrelated to those opponents (*10*, *11*).

Third-party knowledge extends to dominance relationships. For example, male bonnet macaques (*Macaca radiata*) selectively recruit support from males that outrank both themselves and their opponents (*12*), and female monkeys typically support the higher-ranking of two opponents when they intervene in ongoing conflicts (*4*). These recruitment patterns indicate that monkeys know something about the rank relationship between other group members and prefer high-ranking alliance partners over lower-ranking partners. In playback experiments, female baboons (*Papio cynocephalus*) responded more strongly to sequences of calls that simulated rank reversals between females within their groups than to sequences of calls that fit the existing dominance order. Their reactions suggest that the females were aware of the rank relationships between other females and were surprised when interactions confounded their expectations. Similarly, male baboons' reactions to simulated contests between closely ranked and distantly ranked pairs of males suggest that they can assess the rank distance between other males (*13*).

Primates also monitor the quality of relationships between other group members. Hamadryas baboons (*P. hamadryas*), which form one-male groups, do not attempt to take females from rival males when they see that the male and female have formed close bonds (*14*). Playback experiments conducted on chacma baboons indicate that males keep track of the mate-guarding activities of high-ranking males and respond with alacrity when they hear sequences of vocalizations that suggest that consortships have been disrupted and mating opportunities might be available (*15*). When white-faced capuchin monkeys (*Cebus capucinus*) recruit allies, they take into account the quality of relationships between themselves, their opponents, and potential allies (*16*). They selectively solicit support from group members who have stronger relationships with themselves than with their opponents.

**Fig. 1.** Many primates, like these baboons in the Amboseli basin of Kenya, live in large and complex social groups. Baboons have been studied at multiple sites across Africa for decades.

### The Structure of Social Bonds

Female baboons, macaques, and vervets provide a particularly well-documented example of the complex adaptive design of social relationships. Females in these species remain in their natal groups throughout their lives, whereas males disperse to prevent inbreeding (*17*, *18*). Groups may number 20 to 100 individuals and usually contain multiple matrilines (sets of females related through maternal kinship lines). Females spend a substantial amount of time each day grooming and resting in the company of other group members. Females discriminate among potential partners and show strong biases in favor of close maternal kin (Fig. 2). Recent evidence indicates that nepotistic biases also extend to paternal kin, as females preferentially groom and associate with their paternal half-sisters (*19*–*21*). Paternal kin ties often cut across matrilines.

In the Amboseli Basin of Kenya, some pairs of female baboons, particularly close maternal kin, form close and stable relationships (*22*). Females' preferences for partners are influenced by the quality of their interactions. Females who form enduring social bonds groom more equitably than females who have more ephemeral relationships (Fig. 3), and this pattern holds for both maternal kin and others. We do not know whether females come to groom more equitably as their relationships become stronger or females preferentially maintain close relationships with those who groom them equitably.

Kin biases in behavior are common among animals, but female macaques, baboons, and vervets take nepotism one step further. They form matrilineal dominance hierarchies in which maternal kin occupy adjacent ranks: When they mature, daughters attain ranks just below their mothers, and younger sisters outrank older sisters (*23*). Coalitionary support plays an important role in this process, because immature females are selectively supported by close female relatives when they are involved in conflicts with members of lower-ranking matrilines. Eventually, young females are able to defeat everyone that their mothers can defeat. The importance of maternal support for females is

revealed by what happens when mothers are absent. Small juveniles from high-ranking matrilines can defeat larger juveniles from lower-ranking matrilines when their mothers are nearby, but not when their mothers are some distance away (*24*–*26*). At one site, several female baboons orphaned early in life did not attain the ranks formerly held by their mothers (*27*, *28*).

Dominance relationships among females remain remarkably stable over long periods, even generations (*18*). There is some dispute about whether coalitionary support plays the same role in maintaining dominance ranks among adult females as it does in establishing rank. Females intervene in conflicts among adult females at very low rates, which might mean that coalitions might play little role in maintaining the stability of dominance hierarchies (*29*). However, the low rate of interventions may underestimate their importance. The presence of potential allies (and knowledge of alliance partnerships) may be enough to deter challenges (*30*). Moreover, females sometimes give vocal threats when they witness agonistic interactions. In the Okavango Delta, vocal responses are considerably more common than active intervention and appear to play a similar role (*31*).

### The Function of Social Bonds

Several lines of evidence suggest that affiliative social relationships matter to females. Females preserve time for socializing, even under harsh environmental conditions. In the dry season when food is scarce, female baboons spend more time foraging and moving between feeding sites and less time resting (*32*). However, they do not reduce the amount of time that they spend grooming and interacting peacefully with group members.

Females are strongly affected by the loss of preferred companions. In the Moremi Reserve of the Okavango Delta, where predation rates are high, females who suddenly lost close kin experienced significant increases in glucocorticoid levels (*33*, *34*), indicating increased stress. These females' responses were not simply the result of living through stressful events, because females who were present in the group at the same time, but did not suffer personal losses, were unaffected.

Females make adjustments in their social networks in response to demographic changes within their groups. In the Amboseli basin of Kenya, mothers and daughters form particularly close and enduring social bonds, but relationships among sisters are more variable in strength and stability (*21*, *22*). Pairs of maternal and paternal sisters whose mothers are not present in the group have closer relationships than do sisters whose mothers are present in the group. In Moremi, females also compensate for the loss of favorite partners by adjusting their social networks (*33*). Females who lose close kin devote more time to grooming and expand the number of females that they groom in the weeks after the loss.

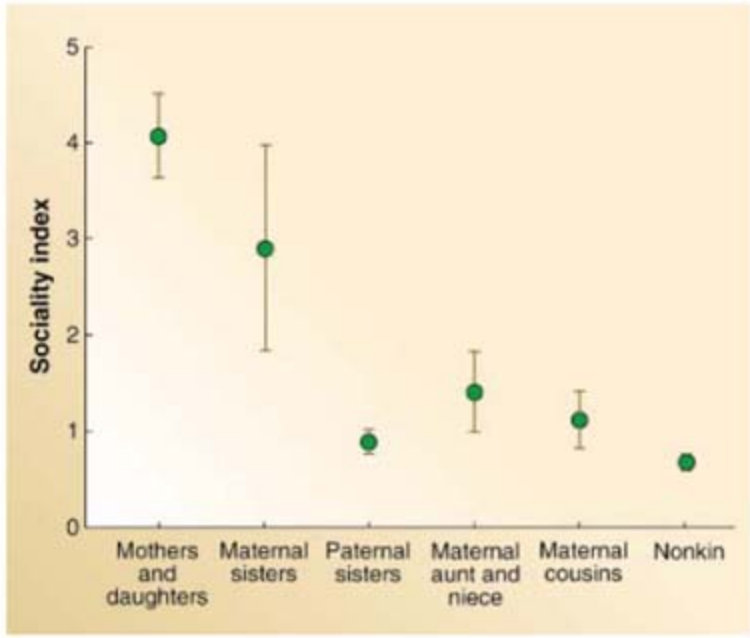


**Fig. 2.** The relationship between maternal and paternal kinship and the strength of social bonds among female baboons. The category of relatedness is plotted on the *x* axis, and the mean and standard error of values of the sociality index are plotted on the *y* axis. The sociality index is a composite measure of dyadic relationship strength based on the frequency of grooming and proximity. [Redrawn from (*22*)]

Further evidence of the importance of social bonds comes from studies of close associations that mothers of newborn infants form with adult males. Mothers are mainly responsible for maintaining proximity to their male associates, and they groom males much more than they are groomed in return (*35*, *36*). Observational data (*35*) and field playback experiments (*36*) indicate that males preferentially protect their female associates from harassment. The value and scope of such protection may vary across sites (*37*). In southern Africa, where immigrant males often kill unweaned infants and infanticide is a major cause of infant mortality (*38*), new mothers are fearful of immigrant males. Lactating females' glucocorticoid levels rise substantially when new males join the group and acquire high-ranking positions (*39*, *40*). However, mothers who have established friendships with adult males experience smaller increases in glucocorticoid levels than do mothers who have not established such associations. In East Africa, infanticide is much less common, but mothers and their offspring may still gain benefits from their associations with adult males. In Amboseli, adult males preferentially support their own juvenile offspring when they are involved in agonistic disputes (*41*).

A direct chain of connections links social bonds to fitness outcomes in primate species with matrilineal dominance hierarchies. Social bonds enhance the prospects for obtaining coalitionary support, coalitionary support affects dominance rank, and dominance rank influences reproductive performance. High-ranking females tend to mature at earlier ages, grow faster, produce healthier infants, have shorter interbirth intervals, and have higher lifetime fitness than low-ranking females (*18*, *42*–*44*). The magnitude of the effects of dominance rank varies over time and across populations. However, any reproductive advantages that high-ranking females accrue will be magnified over time because dominance ranks typically remain stable across generations. High-ranking females will have high-ranking female descendants.

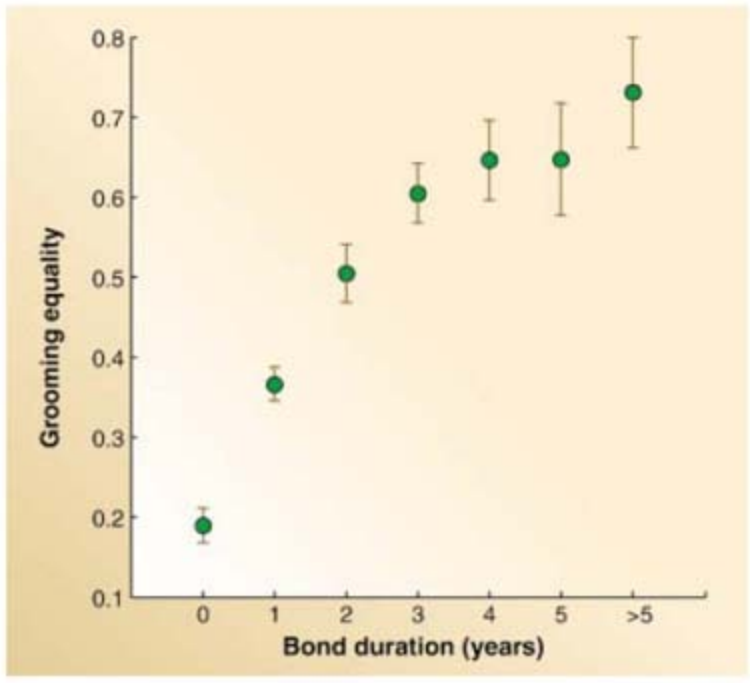


**Fig. 3.** The relationship between grooming equality and bond stability among baboon females. Bond stability is measured as the number of consecutive years in which the same female was among a given female's top three partners (based on the sociality index measure described in Fig. 2). Grooming equality is a measure of the distribution of grooming within dyads, and varies from 0 when grooming is completely one-sided to 1 when grooming is evenly balanced. The mean and standard error of values for adult females are shown. [Redrawn from (*21*)]

For female baboons in Amboseli, the fitness consequences of sociality extend beyond the relationship between dominance rank and reproductive performance (Fig. 4). Females who were more fully socially integrated into their

**Fig. 4.** The mother of a young infant (**center**) is groomed by an adult male (**left**) and another adult female. The female in the center wears a radio collar with an antenna, which allows researchers to locate the group on a regular basis.

groups reproduced more successfully than other females (Fig. 5) (*45*). The positive relationship between sociality and reproductive successs might reflect the fact that some females lived in more favorable habitats or during more favorable time periods than others. These females might have been more social and reproduced more successfully than other females. However, the results remain unchanged when the measures of social integration are corrected to account for group membership and changes in environmental conditions over time. The relationship might also arise because high-ranking females have higher reproductive success and belong to larger matrilines than lower-ranking females do. Again, the relationship between social integration and reproductive success remains significant when dominance rank and lineage size are controlled statistically.

There may be similar connections between sociality and fitness outcomes in other primate taxa, although the evidence is less complete. For example, females living in groups of red howler monkeys (*Alouatta seniculus*) with more close kin had higher reproductive success than females living in groups with fewer close kin (*46*). It is not entirely clear why females benefit from living with close kin. Howler monkeys collectively defend their territories and practice extensive allomaternal care, and it is possible that related females cooperate more effectively in intergroup encounters or provide better care for one another's infants.

Male chimpanzees (*Pan troglodytes*) provide an interesting parallel to philopatric female baboons (Fig. 6). Males remain in their natal groups throughout their lives, whereas females usually disperse (*47*). Chimpanzees form fission/fusion communities and frequently break up into smaller parties. Like female baboons, males spend considerable amounts of time grooming one another and spend much of their time in the company of other males. Male chimpanzees also participate in a number of collective activities, including territorial patrols, coalitionary aggression, cooperative hunting, food sharing, and joint mate-guarding. Males that groom one another often also participate in collective activities together, indicating that males form strong and well-differentiated relationships with one another. At Ngogo in Uganda, male chimpanzees preferentially groom, associate, support, share food, and patrol with their maternal brothers but do not show similar preferences for paternal brothers (*48*).

Males may gain important benefits from the relationships that they form with other males. Males compete intensely for high-ranking positions within their groups, and males' ability to obtain and maintain high rank is influenced by their ability to recruit support from other males (*47*). Although the political maneuverings of chimpanzees may be more complicated than the nepotistic strategies of female baboons, the result is much the same. High-ranking male chimpanzees have priority of access to receptive females and can prevent other males from mating (*47*). Genetic analyses confirm that the top-ranking male sires a disproportionate number of infants (*49*, *50*). Social relationships among male chimpanzees may also enhance the fitness of lower-ranking males. In one community, the alpha male selectively tolerated mating attempts by his allies. As a consequence, the mating success of males was more closely related to how often they supported the alpha male than to their own dominance rank (*51*).

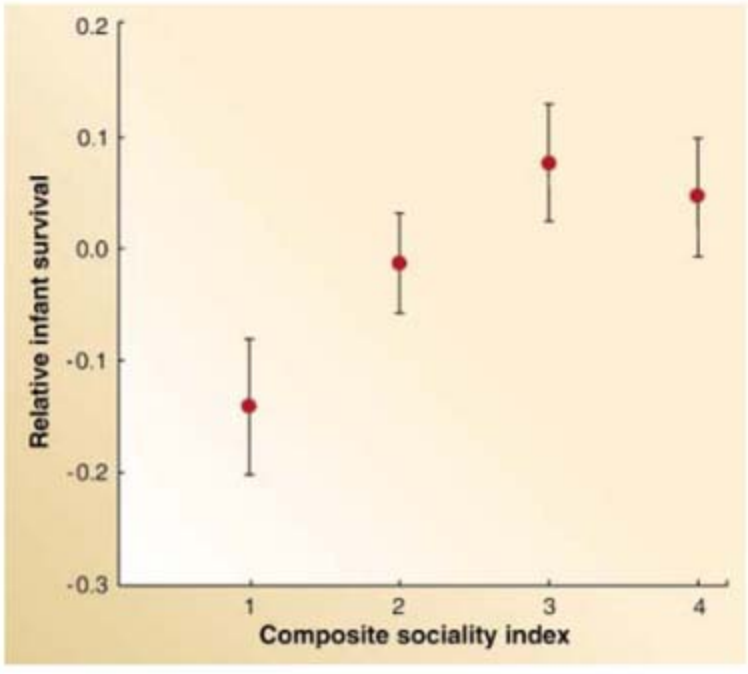


**Fig. 5.** The relationship between social integration and reproductive success among baboon females. For each female, a composite sociality index was computed. This value represented the frequency of grooming and proximity to all adult partners. Here, composite scores were ranked and divided into quartiles. The mean and standard error of the sociality index for the least social females are on the left, and those for the most social females are on the right. Infant survival is based on the proportion of infants that survived to 1 year of age, a major component of variation in females' lifetime fitness. [From (*45*)]

## Future Directions

The work summarized here suggests that variation in the quality of social bonds has fitness consequences for individuals in some primate species. For many primate species, our knowledge about the structure and function of social bonds is much less complete. These gaps create difficulties when we try to compare the impact of sociality on fitness in species that live in groups of different size and configurations, or to compare the extent of social complexity across species.

It may be profitable to extend these kinds of analyses to other taxa in which group size is linked to relative brain size, such as cetaceans, carnivores, insesctivores, and ungulates (*2*). Moreover, it is important to recognize that primates have not cornered the market on social complexity. For example, spotted hyenas (*Crocuta crocuta*) establish matrilineal dominance hierarchies, form coalitions, reconcile after conflicts, recognize paternal kin, hunt cooperatively, and recognize third-party relationships (*52*); an African elephant (*Loxodonta africanus*) can recognize the vocal-

**Fig. 6.** Two adult male chimpanzees in Kanawara groom. Male chimpanzees participate in a variety of cooperative activities and form close social bonds. [Photograph taken by Ian Gilby]

izations of at least 100 other individuals (*53*); bottlenosed dolphins (*Tursiops aduncus*) form stable multilevel alliances (*54*); and rooks (*Corvus frugilegus*) console their partners after conflicts with other members of their flocks (*55*). For individuals in these species, there may also be important social components of fitness.

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56. My ideas about the adaptive value of social bonds have been profoundly influenced by my collaborations with S. Alberts, J. Altmann, D. Cheney, and R. Seyfarth. This paper has profited from conversations with and comments from them as well as R. Boyd, N. Clayton, T. Clutton-Brock, N. Emery, and K. Langengraber.

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REVIEW

# Prospection: Experiencing the Future

**Daniel T. Gilbert[1]* and Timothy D. Wilson[2]**

All animals can predict the hedonic consequences of events they've experienced before. But humans can predict the hedonic consequences of events they've never experienced by simulating those events in their minds. Scientists are beginning to understand how the brain simulates future events, how it uses those simulations to predict an event's hedonic consequences, and why these predictions so often go awry.

All animals are on a voyage through time, navigating toward futures that promote their survival and away from futures that threaten it. Pleasure and pain are the stars by which they steer. When animals experience pleasure they hold a steady course, and when they experience pain they tack. With a bit of practice, most animals learn to associate pleasures and pains with their antecedents—the smell of an approaching predator or the call of a beckoning mate—which enables them to steer toward pleasure and away from pain before they actually experience either. When a mouse hides before a cat enters the room it is responding to an event that has not yet happened, and its ability to do so is one of evolution's most remarkable achievements.

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Humans have this ability too. But they also have another ability that extends their powers of foresight far beyond those of any other animal. Just as retrospection refers to our ability to re-experience the past, prospection refers to our ability to "pre-experience" the future by simulating it in our minds. We know that chocolate pudding would taste better with cinnamon than dill, that it would be painful to go an hour without blinking or a day without sitting, that winning the lottery would be more enjoyable than becoming paraplegic—and we know these things not because they've happened to us in the past, but because we can close our eyes, imagine these events, and pre-experience their hedonic consequences in the here and now. Unfortunately, the conclusions that we draw in this way aren't always right. Trysts are often better contemplated than consummated, and sweetbreads are often better the other way around. In this article we will review what scientists have discovered about how humans mentally simulate future events and how well they can predict their hedonic reactions to them.

### Mechanisms of Prospection

The brain combines incoming information with stored information to build "mental representations," or internal models, of the external world. The mental representation of a past event is a memory, the mental representation of a present event is a perception, and the mental representation of a future event is a simulation. One way to predict the hedonic consequences of a future event is to simulate it, and the brain's frontal regions appear to play a critical role in that process (*1*–*3*). Patients with damage to the prefrontal cortex are described as being "bound to present stimuli" (*4*) and "locked into immediate space and time" (*5*). Such patients seem unable to simulate future events and often have difficulty answering simple questions such as "What will you be doing tomorrow?" (*6*–*8*). Neuroimaging studies reveal that both the prefrontal cortex and the medial temporal lobes are strongly activated by prospection (*9*–*11*). Interestingly, these regions are part of the "default network" that is active when people are not specifically engaged in other tasks (*12*), which suggests that when the mind is not busy perceiving the present it tends to simulate the future (*13*). The critical role played by frontal regions suggests that few if any other animals are able to simulate future events, and even our closest relatives in the animal kingdom may be "stuck in time" (*14*, *15*). Although some animals have evolved strategies to solve problems involving future events such as impending food shortages (*16*), it seems unlikely that they achieve these solutions by simulating future events. Indeed, the ability to simulate and pre-experience the future does not appear in human children until the third or fourth year of life, long after other complex intellectual abilities such as language have bloomed (*17*).

People mentally simulate future events, but how do they use those simulations to predict the event's hedonic consequences? As the mere thought of eating a liver popsicle reveals, mental simulations of the future can elicit hedonic reactions in the present (*18*, *19*). People use their immediate hedonic reactions to simulations as predictors of the hedonic reactions they are likely to have when the events they are simulating actually come about (*20*–*22*). People do not imagine feeling anxious while having a colonoscopy so much as they imagine a colonoscopy, feel anxious, and then take this anxiety as an indicator of the feelings they can expect to experience during the procedure itself. Simulations allow people to "preview" events and to "prefeel" the pleasures and pains those events will produce. A great deal has been learned in the past few years about the neural substrates of prefeeling. For example, it appears that the activity of midbrain dopamine neurons encodes information about the magnitude of pleasure that a future event is likely to produce (*23*–*25*). Simulation of pleasurable future events activates subcortical structures such as the nucleus accumbens (*26*) and the anterior regions of the ventral striatum (*27*), whereas simulation of painful future events activates the amygdala (*28*) and/or the posterior ventral striatum (*27*). An extensive body of research shows that prefeeling depends critically on the ventromedial prefrontal cortex and that people with damage to this area find it difficult to predict the hedonic consequences of future events (*29*). Although there is still much to learn about its neural substrates, prefeeling clearly provides a basis for making hedonic predictions.

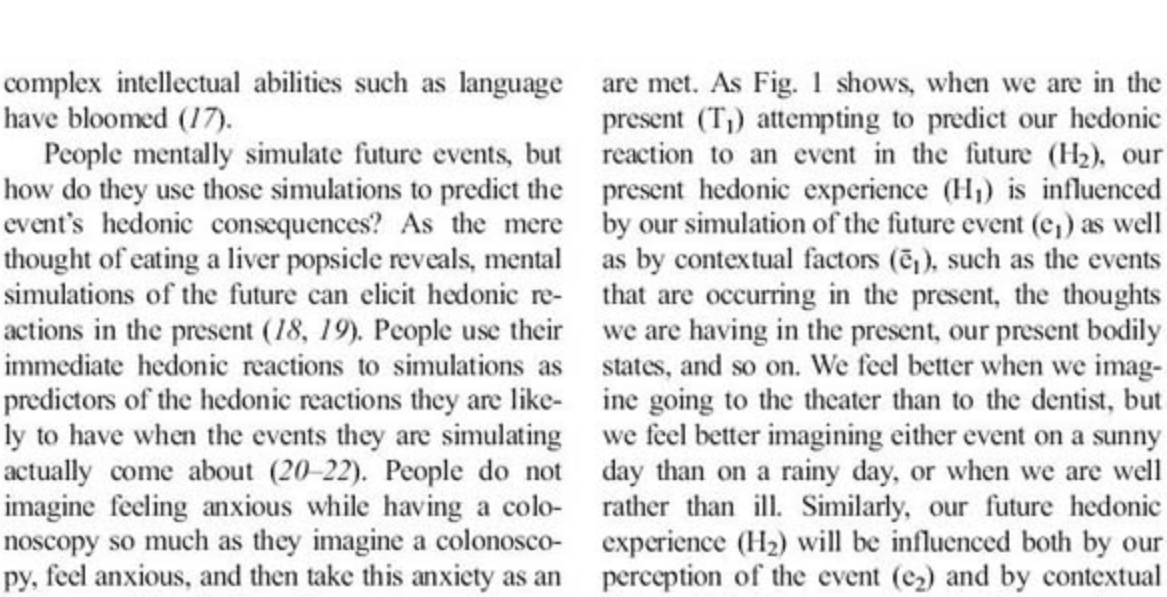


**Fig. 1.** Hedonic experience is influenced by mental representations (simulations and perceptions) and by contextual factors.

### Errors of Prospection

Prefeelings will be reliable predictors of subsequent hedonic experiences when two conditions are met. As Fig. 1 shows, when we are in the present ($T_1$) attempting to predict our hedonic reaction to an event in the future ($H_2$), our present hedonic experience ($H_1$) is influenced by our simulation of the future event ($e_1$) as well as by contextual factors ($\bar{e}_1$), such as the events that are occurring in the present, the thoughts we are having in the present, our present bodily states, and so on. We feel better when we imagine going to the theater than to the dentist, but we feel better imagining either event on a sunny day than on a rainy day, or when we are well rather than ill. Similarly, our future hedonic experience ($H_2$) will be influenced both by our perception of the event ($e_2$) and by contextual factors ($\bar{e}_2$). Because our hedonic experiences are influenced both by our mental representation of the event and by contextual factors, our present hedonic experience will be a reliable predictor of our future hedonic experience if and only if (i) our simulation of the event at $T_1$ exerts the same influence on our hedonic experience at $T_1$ as our perception of the event at $T_2$ exerts on our hedonic experience at $T_2$, and (ii) contextual factors at $T_1$ exert the same influence on our hedonic experience at $T_1$ as contextual factors at $T_2$ exert on our hedonic experience at $T_2$. In other words, $H_1 = H_2$ if and only if $e_1 = e_2$ and $\bar{e}_1 = \bar{e}_2$. Errors in prospection arise from the fact that people use their prefeelings to make hedonic predictions even when one or both of these conditions is not met. These errors are of four kinds.

*Simulations are unrepresentative.* We naturally imagine our next dental appointment by remembering our last one. Memories are the building blocks of simulations (*13*, *30*–*33*), which is why amnesiacs who have trouble with retrospection tend to have trouble with prospection as well (*7*, *8*, *34*). Of course, simulations cannot accurately represent the future if they are constructed from memories that don't accurately represent the

past, and research suggests that people often use unrepresentative memories as a basis for simulation. For example, when people who have missed trains in the past are asked to imagine missing a train in the future, they tend to remember their worst train-missing experience rather than their typical train-missing experience. They then use this unrepresentative memory to construct a simulation of their next train-missing experience, which leads them to overestimate how painful the next train-missing experience will be (*35*). Similarly, when people experience an unpleasant episode that ends in brief relief—for example, submerging their arms for 90 s in a bath of ice water that is slightly warmed in the final 30 s—they tend to remember the closing moments of the experience rather than the most typical moments. They then use this unrepresentative memory to construct a simulation of the event's recurrence, which leads them to underestimate how painful the recurrence will be (*36*, *37*). It seems that everyone remembers their best day, their worst day, and their yesterday. Because unusual events and recent events are so memorable, people tend to use them when constructing simulations of future events.

*Simulations are essentialized.* When we imagine "going to the theater next week," we don't imagine every detail of the event, but rather, we imagine the essential features that define it. We imagine seeing a stage filled with actors but we do not imagine parking the car, checking our coat, or finding our seat. The problem with omitting inessential features from simulations is that such features can profoundly influence our subsequent hedonic experience. Most events have a small set of extremely positive or negative essential features that define them, as well as a large set of both mildly positive and mildly negative inessential features that don't. The event's net hedonic effect is a weighted average of these. Because simulations omit inessential features, people tend to predict that good events will be better and bad events will be worse than they actually turn out to be (*38*). The young couple who simulate the joys of parenthood but fail to simulate the drudgery of diapers are unlikely to have the hedonic experience they imagined.

The tendency for simulations to omit inessential features becomes more pronounced as the event being simulated becomes more temporally distant (*39*, *40*). Participants in one study were told that in a year there would be an interesting lecture at an inconvenient location and a boring lecture at a convenient location. Because their simulations of the lecture contained the essential features (e.g., the topic) but lacked the inessential features (e.g., the location), participants predicted that they would attend the more interesting lecture. But participants who were told that the same lecture was taking place tomorrow instead of next year tended to simulate both the essential and inessential features, and thus predicted that they would attend the more convenient lecture (*41*). The fact that simulations of far-future events are especially likely to omit inessential features is one of the reasons why people so often make future commitments that they regret when the time to fulfill them arrives.

*Simulations are abbreviated.* If we imagined each and every moment of the events we were simulating, our simulations would take as long as the events themselves. Simulations are naturally abbreviated and represent just a few, select moments of a future event. The moments they select tend to be the early ones. When people imagine what their lives would be like if they won the lottery or became paraplegic, they are more likely to imagine the first day than the two-hundred-and-ninety-seventh. The problem with imagining only the early moments of an event is that hedonic reactions to events typically dissipate over time, which means that mental simulations tend to overrepresent the moments that evoke the most intense pleasure or pain. This is one of the reasons why healthy people consistently underestimate how happy they would be in various states of ill-health (*42*–*44*). When people imagine "losing mobility," they expect to be less happy than people who have experienced these events actually are because their simulations overrepresent the initial—and typically the worst—moments of these events. The tendency to underestimate how quickly we will adapt to a wide range of pleasurable and painful events is probably the most commonly observed error in research on hedonic prediction (*45*).

Adaptation takes time, and because simulations do not fully "play out" the events they represent, people's hedonic predictions are typically unaffected by those features of an event that will promote or inhibit adaptation over time (*46*–*49*). For example, people adapt to events much more quickly when they understand why those events happened. When students at a university library were approached by a researcher and given a $1 coin, those who received an explanation for the event were less happy 20 min later than those who did not (Fig. 2). But when students were asked to simulate the event, they predicted that they would be happier if they received an explanation (*50*). Participants in another study were more satisfied with a gift when they were not given the opportunity to exchange it because inescapability, like explanation, facilitates adaptation. And yet, participants who merely simulated receiving gifts failed to realize that they would be more satisfied with gifts that they couldn't exchange (*48*). Because simulations tend to represent the early mo-


**Fig. 2.** When students in a library were given a card with a $1 coin attached, they were in better moods 20 min later if they received the top card than the bottom card; however, when asked to simulate this event, students predicted that they would be in better moods if they received the bottom card than the top card (*50*). The bottom card is identical to the top card except that it includes the phrases "Who are we?" and "Why do we do this?" The inclusion of these phrases creates a question-and-answer format that gives people the sense that the event has been explained. The histograms show the average predicted and experienced mood as measured on a series of nine-point Likert-type rating scales.

ments of future events, predictions based on them tend to ignore things that happen in the later moments.

*Simulations are decontextualized.* As mentioned earlier, two conditions must be met for a person's present hedonic experience to be a reliable predictor of their future hedonic experience. First, their simulation of an event ($e_1$) must exert the same influence on their present hedonic state ($H_1$) as their perception of the event ($e_2$) will exert on their future hedonic state ($H_2$). This does not always happen because compared to perceptions, simulations are unrepresentative, essentialized, and abbreviated. The second condition that must be met is that contextual factors ($\bar{e}_1$) must exert the same influence on their present hedonic state ($H_1$) as contextual factors ($\bar{e}_2$) will exert on their future hedonic state ($H_2$). Unless $T_1$ and $T_2$ are brief and contiguous, this is unlikely to happen because contextual factors—from the temperature in a room to the amount of glucose in a bloodstream—change over time.

Research shows that people often do not consider the potentially significant differences between contextual factors at $T_1$ and $T_2$ when using their present hedonic state to predict their future hedonic state (*51*). For example, hungry people mistakenly expect to like eating spaghetti for breakfast the next day, and sated people mistakenly expect to dislike eating it for dinner the next day (*52*). People who have just exercised mistakenly expect to enjoy drinking water the next day more than do people who are about to exercise (*53*). In both cases, people do not seem to realize that their present hunger and thirst are influencing their hedonic reactions to simulated future consumption. They ignore the fact that the contextual factors that are presently exerting an influence at $T_1$ (i.e., hunger and thirst) will not exert the same influence at $T_2$. Conversely, people overestimate how unhappy they will be after their team loses a football game (*54*) and how happy they will be after becoming wealthy (*55*) because they do not consider the fact that their hedonic experience after an athletic defeat or a financial victory will be influenced by factors other than scoreboards and bank balances. They ignore the fact that the contextual factors that will exert an influence at $T_2$ (e.g., weather, traffic, conversation, etc.) are not presently exerting an influence at $T_1$ (*56*). And indeed, when people are specifically encouraged to consider these contextual factors, their predictions become more accurate (*54*, *57*).

## Conclusion

Mental simulation is the means by which the brain discovers what it already knows. When faced with decisions about future events, the cortex generates simulations, briefly tricking subcortical systems into believing that those events are unfolding in the present and then taking note of the feelings these systems produce. The cortex is interested in feelings because they encode the wisdom that our species has acquired over millennia about the adaptive significance of the events we are perceiving. Alas, actually perceiving a bear is a potentially expensive way to learn about its adaptive significance, and thus evolution has provided us with a method for getting this information in advance of the encounter. When we preview the future and prefeel its consequences, we are soliciting advice from our ancestors.

This method is ingenious but imperfect. The cortex attempts to trick the rest of the brain by impersonating a sensory system. It simulates future events to find out what subcortical structures know, but try as it might, the cortex cannot generate simulations that have all the richness and reality of genuine perceptions. Its simulations are deficient because they are based on a small number of memories, they omit large numbers of features, they do not sustain themselves over time, and they lack context. Compared to sensory perceptions, mental simulations are mere cardboard cut-outs of reality. They are convincing enough to elicit brief hedonic reactions from subcortical systems, but because they differ from perceptions in such fundamental ways, the reactions they elicit may differ as well. Although prospection allows us to navigate time in a way that no other animal can, we still see more than we foresaw.

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# Leptin Regulates Striatal Regions and Human Eating Behavior

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Leptin is an adipocyte-derived circulating hormone that provides information to the brain about energy stores (*1*). The brain's response to leptin involves changes in energy expenditure and food intake. Leptin-deficient mammals, including humans, are markedly hyperphagic, and leptin replacement reverses this. However, there is little information about how higher brain centers integrate homeostatic signals such as leptin with images of nonfood in the leptin-deficient and leptin-treated states. We used 10-cm visual analog scores to rate hunger, satiety, and the "liking" of food images (*2*). To examine the interaction with eating, we studied participants in fasted and fed states (*2*).

After leptin treatment, hunger ratings in the fasted state decreased, and satiety following a meal increased (*2*). Whereas visual images of food elicited no differential activation of mesolimbic areas between stimulus type, fasting state, and leptin (Fig. 1D and fig. S1A).

In the leptin-deficient state, accumbens-caudate activation correlated positively with liking ratings in fasted ($P < 0.05$) and fed ($P < 0.05$) states (Fig. 1D). In the leptin-treated state, accumbens-caudate activation correlated positively with liking ratings only in the fasted state ($P < 0.05$), an effect that was also seen in normal weight controls studied using the same paradigm (fig. S1B).

We have shown that leptin markedly affects neural responses to visual food stimuli. In patients with congenital leptin deficiency, leptin administration results in an increased ability to discriminate between the rewarding properties of food and, at the neuronal level, in the modulation of activation in the ventral striatum. This interaction suggests that leptin modulates feeding-related mesolimbic sensitivity to visual food stimuli. Our findings are consistent with the view that activation in the ventral striatal region does not directly encode the "liking" but rather the motivational salience or "wanting" of food (*4*). In the leptin-deficient state, images of well-liked foods engender a greater wanting response, even when the subject has just been fed. After leptin treatment, well-liked food images engender this response only in the fasted state, an effect consistent with the response in control subjects. Thus, wanting of food appears to drive the correlation between ventral striatal activation and liking.

Our data support the notion that leptin acts on neural circuits governing food intake to diminish perception of food reward while enhancing the response to satiety signals generated during food consumption. These experiments thus provide functional neuroanatomical insights into the mechanisms by which leptin, the key peripherally derived signal encoding nutritional state, can interact with stimuli related to the visual appearance and the recent ingestion of food to modulate spontaneous eating behavior in humans.

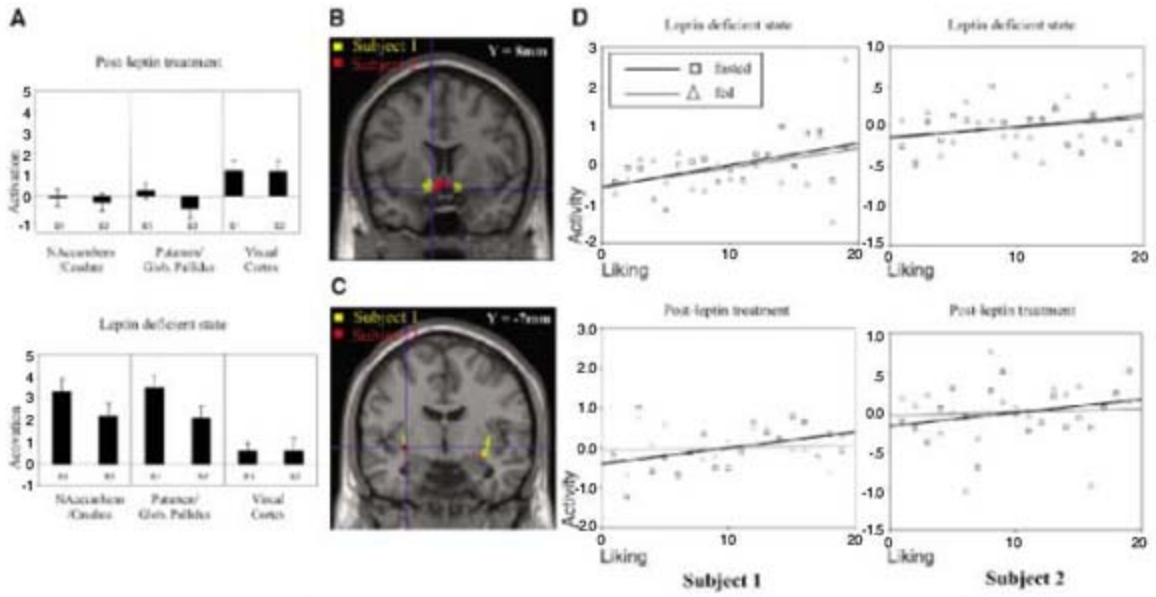


**Fig. 1.** Leptin regulates brain responses to food images. (**A**). Leptin reduces activation in the nucleus accumbens-caudate and putamen–globus pallidus regions in subject 1 (S1) and subject 2 (S2) (linear regression coefficients; mean ± SE). Visual cortex showed no response to leptin. (**B**) Nucleus accumbens-caudate and (**C**) putamen–globus pallidus are activated by food stimuli (threshold $P < 0.05$; corrected for multiple comparisons). (**D**) A three-way interaction between stimulus (food versus nonfood images), fasted or fed state, and leptin localized to nucleus accumbens-caudate (fig. S1A). Mean corrected activity from this region (*y* axis) is plotted against the ranked liking for foods. Each block comprised five foods; mean liking ratings for each block were ranked and plotted against nucleus accumbens-caudate activity for that block in the fasted (black) and fed (gray) states, pre- and postleptin. Before leptin treatment, activation in nucleus accumbens-caudate correlated positively with liking in both fasted ($P < 0.05$) and fed ($P < 0.05$) states. After leptin treatment, activation correlated with liking ratings only in the fasted state ($P < 0.05$).

the rewarding properties of food. We studied a 14-year-old boy (subject 1) and a 19-year-old girl (subject 2) with the very rare condition of congenital leptin deficiency, before and after 7 days of treatment with recombinant human leptin (*2*). Although no changes in body weight were seen over this time, leptin treatment had a major effect on food intake. Ad libitum energy intake at a test meal was reduced from 152 to 64 kJ/kg of lean mass and from 169 to 98 kJ/kg of lean mass in subjects 1 and 2, respectively [normal ad libitum intake was 54 ± 12 kJ/kg of lean mass (± SD) in age-related controls (*3*)]. We used functional magnetic resonance imaging (fMRI) to measure differential brain activation by visual images of food compared with in the leptin-replaced state, the leptin-deficient state was associated with marked activation in the anteromedial ventral striatum (nucleus accumbens and caudate nucleus) and posterolateral ventral striatum (putamen and globus pallidus) (Fig. 1, A to C).

When asked to rate how much they liked each of the food images, leptin-deficient subjects in the fed state gave high ratings to all food images (mean = 8.9 ± 0.5). After leptin, the liking ratings were reduced (mean = 5.9 ± 0.4). These behavioral responses were accompanied by a region-specific change in the evoked neural response after leptin treatment. The ventral striatum (localized to nucleus accumbens-caudate nucleus) was identified as the site of an interaction


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### Supporting Online Material

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Figs. S1 and S2
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# Bilayer $^3$He: A Simple Two-Dimensional Heavy-Fermion System with Quantum Criticality

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Two-dimensional helium-3 ($^3$He) provides a simple model for the experimental investigation of the emergence of quantum complexity in a strongly correlated Fermi system. We have observed two-dimensional, two-band heavy-fermion behavior in bilayer films of $^3$He atoms when adsorbed on the surface of graphite preplated by a solid bilayer of $^4$He. Thermodynamic measurements on this system showed that the relevant control parameter is the total density of the $^3$He film. The $^3$He bilayer system can be driven toward a quantum critical point at which the effective mass appears to diverge, interband coupling vanishes, and a local-moment state appears. It opens a new testing ground for theories of quantum criticality in heavy-fermion materials.

Quantum critical points (QCPs) occur when a material can be smoothly tuned with the application of an external control parameter between competing ground states at the absolute zero of temperature (*1*, *2*). Their importance arises because the quantum fluctuations seen at low temperatures can exert a profound influence on material properties at higher temperatures (*3*). The heavy-fermion f-electron alloys provide important examples of such quantum criticality (*4*). In these systems, a lattice of f-electron moments couple to the conduction electrons via the Kondo interaction; at low temperatures, this results in a large Fermi surface incorporating the f-electrons. The large effective mass of the quasi-particles arises from the release of the spin entropy of the localized moments. In such Kondo-lattice materials, external control parameters such as pressure or magnetic field can be used to tune to magnetic QCPs. However, the theoretical understanding of quantum criticality in these systems is a matter of controversy (*5*, *6*). In different scenarios, the transition from the heavy-fermion state to antiferromagnetic order can involve the breakdown of the Kondo effect and a sudden transformation of the Fermi surface at the QCP, or the formation of a spin density wave. The mechanism by which the breakup of quasi-particles near the QCP occurs, the nature of the quantum fluctuations (local or itinerant), and the relative importance of spin and charge degrees of freedom are all areas of active investigation.

The $^3$He atom has nuclear spin $S = ½$; the interatomic potential consists of a strong hard-core repulsion and a weakly attractive tail. Bulk liquid $^3$He is the paradigm for strongly correlated fermions, and it played an important role in establishing Landau Fermi-liquid theory as the standard theoretical model for these systems (*7*, *8*). We report evidence for the emergence of heavy-fermion quantum criticality in a fluid bilayer of $^3$He, a system that is simpler than the intermetallic compounds that have previously been the central focus of attention.

**Background: $^3$He films on graphite.** Two-dimensional (2D) $^3$He has been extensively studied through measurements on atomically layered helium films grown on the surface of graphite (*9*). Particular attention has been given to the second layer of $^3$He, which is grown on top of a dense solid first $^3$He layer that forms a triangular lattice with a density of 11.2 atoms/nm$^2$. At sufficiently low coverage, the second layer of $^3$He forms a 2D fluid, and at low temperatures, both its heat capacity (*10*) and magnetization (*11*, *12*) display the expected features of a Landau Fermi liquid. At higher coverage, the second $^3$He layer solidifies. Stabilized by the weak periodic potential arising from the solid first layer, the second-layer 2D solid forms a $\sqrt{7} \times \sqrt{7}$ triangular superlattice (*10*) at a ratio of 4/7 between second- and first-layer densities, corresponding to a second-layer density of 6.4 nm$^{-2}$. The same superlattice structure is observed if the first $^3$He layer is replaced by a monolayer of $^4$He (*13*) or by a bilayer of hydrogen deuteride (*14*). In the latter case, the density of the $\sqrt{7} \times \sqrt{7}$ triangular superlattice is 5.2 nm$^{-2}$. Upon approaching the density of this superlattice by increasing the $^3$He coverage of the second-layer fluid film, an apparent divergence of the effective quasi-particle mass has been observed; this was interpreted as a density-driven Mott-Hubbard transition upon approaching half-filling of the superlattice (*15*).

It is established that the second-layer solid (Mott insulator) phase is a frustrated 2D magnetic system of $S = ½$ local moments on a triangular lattice. Frustration arises both from the lattice geometry and from competing intralayer atomic ring exchange interactions (*16*, *17*). This exchange gives rise to a low-temperature heat capacity maximum due to short-range magnetic order at $T \sim J_c$, where $J_c$ is an effective exchange constant. As expected theoretically, no magnetic ordering transition is observed at finite temperature in this 2D system. Upon increasing the $^3$He coverage further, a fluid overlayer forms and the second-layer solid is compressed somewhat. The competing exchange interactions are a function of the total coverage and may be determined experimentally (*18*, *19*). In this way, the magnetic ground state may be tuned with coverage from quantum spin liquid to ferromagnetic (*20*) through intermediate states that are not fully understood.

In the present experiment, we preplate the graphite surface with two atomic layers of solid $^4$He (*21*) (Fig. 1, inset). The properties of a $^3$He film grown on this surface are studied through measurements of heat capacity and magnetization as a function of coverage, over the temperature range 1 to 100 mK (*22*). The key feature of the $^3$He bilayer adsorbed on this composite substrate is that we create a delicately balanced system of two strongly coupled fluid layers of $^3$He, the first of which is on the verge of localization.

**Overview: $^3$He bilayer.** Figure 1 is a simplified phase diagram of a $^3$He film grown on the graphite/$^4$He/$^4$He substrate. The first layer of $^3$He (L1) initially forms a monolayer fluid. With increasing coverage, a second layer (L2) forms that is also fluid. The resultant $^3$He fluid bilayer comprises an almost localized layer (L1) and an overlayer of itinerant fermions (L2); these layers are coupled together by particle exchange. Below a characteristic temperature $T_0$, this fluid bilayer has Fermi-liquid properties, with an enhanced quasi-particle mass. The effective mass of the heavy-fermion state at $T \ll T_0$ increases with coverage, with an apparent divergence at a critical coverage $n_c$, at which $T_0$ collapses. Beyond this coverage, L1 is fully localized at all temperatures investigated, and the two layers decouple. The system then comprises a solid $^3$He layer (L1) forming a $S = ½$ magnet on a triangular lattice, and a fluid overlayer (L2) with relatively weak correlations and moderate quasi-particle effective mass.

**Monolayer film.** At coverage $n < 6.3$ nm$^{-2}$, the film consists of a single atomic layer of $^3$He. The heat capacity (fig. S5) is of the form $c(T) = \beta + \gamma T + \Gamma T^2$, where the leading order correction to Fermi liquid theory $\Gamma < 0$, as found previously for fluid monolayers on a different substrate (*15*). We may infer the effective mass from the linear term in the heat capacity, $\gamma$ (*23*). Over the coverage range 4.0 to 6.0 nm$^{-2}$, the effective mass ratio $m^*/m$ shows a modest increase from 2.8 to 3.9. The term $\beta$ is a small apparent offset in the heat capacity observed at the lowest temperatures, similar to that found

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in previous work (*10*). This term is conventionally attributed to a small proportion of $^3$He atoms localized by weak substrate heterogeneity (fig. S4).

**$^3$He bilayer: Heavy-fermion phase.** Heat capacity isotherms show that promotion to a second $^3$He layer (L2) occurs at a total coverage $n = 6.3 \pm 0.2$ nm$^{-2}$ ($P_{L2}$ in Fig. 1). As the fluid bilayer forms, the most striking feature that develops is a maximum in the heat capacity (Fig. 2A, inset). The temperature of this maximum, $T_0$, depends strongly on the density of layer L2; $T_0$ decreases with increasing $^3$He coverage. Between 7.5 and 9.0 nm$^{-2}$, $T_0$ decreases from 58 to 12 mK (*24*). The appearance of this qualitatively new effect in $^3$He films is strongly indicative of interlayer coupling between L1 and L2.

In Fig. 2A, we plot the heat capacity $c(T)$ and $\gamma(T) = [c(T) - \beta]/T$ as a function of temperature. Only well below $T_0$ does $\gamma(T)$ tend to an approximately constant value, as expected for a Fermi liquid. In this regime, we infer an effective mass ratio $m^*/m$ from a determination of $\gamma(T \rightarrow 0)$. Describing the heat capacity at $T < T_0$ requires the inclusion of a thermally activated term in the heat capacity such that $c(T) = \beta + \gamma_1 T + \gamma_2 \exp(-\Delta/T)$, introducing a "pseudogap" $\Delta$. Alternative fit functions (fig. S6) yield consistent values of the parameter $\gamma_1$. The effective mass inferred from $\gamma_1$ shows a pronounced increase with increasing coverage. The largest value observed directly is $m^*/m = 18.9$ at a coverage of 9.0 nm$^{-2}$. These observations show that a heavy-fermion state of the bilayer develops below the characteristic temperature $T_0$ (region A of phase diagram, Fig. 1).

The heavy-fermion picture is supported by measurements of the nuclear magnetization. Figure 2B shows the total sample magnetization $M$ as measured by field-swept continuous-wave nuclear magnetic resonance (NMR) in a static field of $B = 28$ mT (*25*). For coverages below 9.0 nm$^{-2}$, $M$ is proportional to the uniform magnetic susceptibility of the fermionic system. It exhibits a

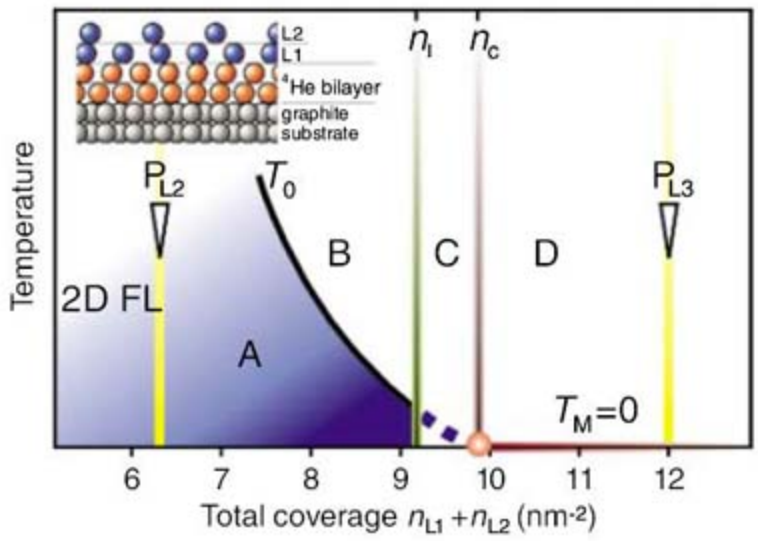
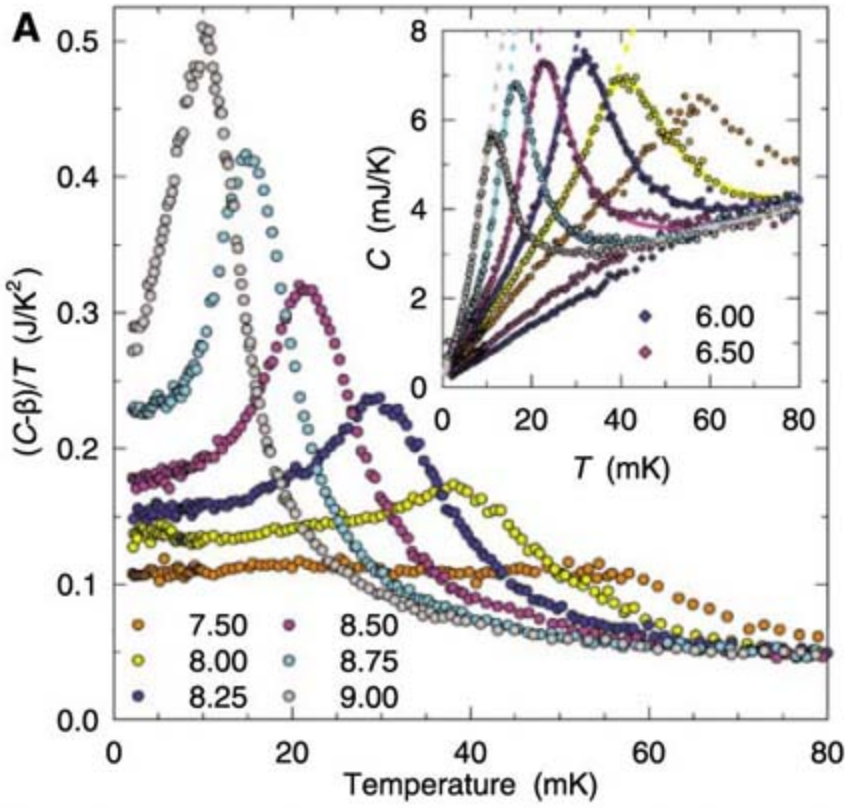



**Fig. 1.** Proposed phase diagram of $^3$He film adsorbed on graphite plated by a bilayer of $^4$He. $P_{L2}$ indicates formation of the $^3$He bilayer. Region A: $T < T_0$. L1 and L2 form a two-band heavy-fermion system. Region B: $T > T_0$. The two layers progressively decouple into a strongly correlated, nearly localized narrow-band Fermi system (L1) and a weakly correlated 2D Fermi fluid (L2). Region C: $n_1 < n < n_c$, intervening phase. Region D: The two layers decouple into a 2D local-moment magnet (Mott insulator, L1) with frustrated intralayer spin exchange and no magnetic phase transition at finite temperature, $T_M = 0$, and a weakly correlated 2D Fermi fluid overlayer (L2). $P_{L3}$ indicates the formation of a third $^3$He layer. Inset is a schematic of the bilayer $^3$He system (see text for details).



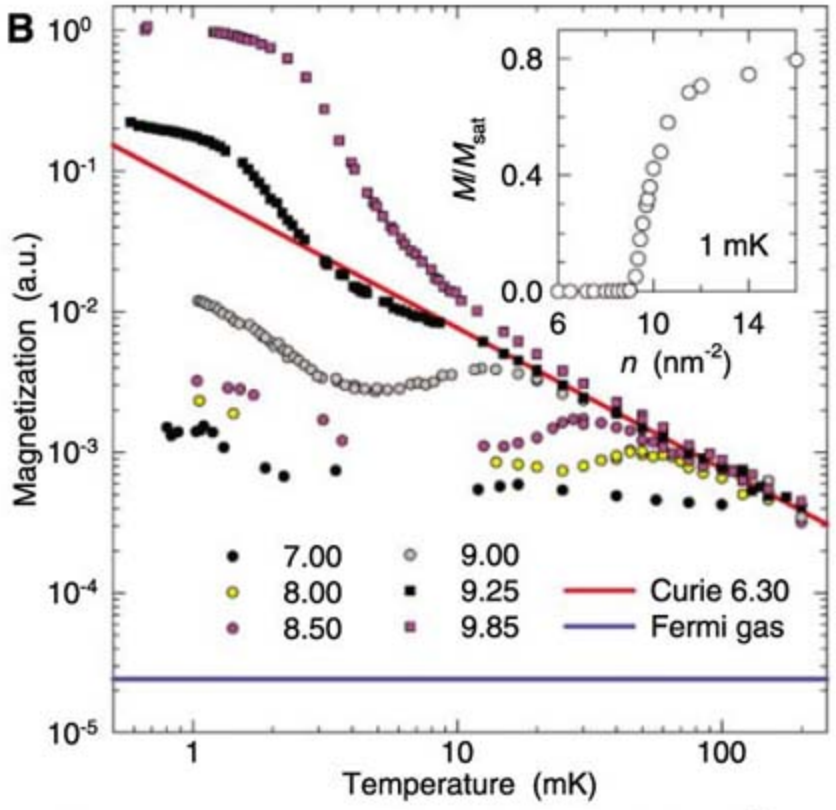




**Fig. 2.** Heat capacity and magnetization data for a series of coverages (nm$^{-2}$) corresponding to a bilayer fluid film, L1 + L2. (**A**) Heat capacity divided by temperature, $\gamma(T)$, after subtraction of a small offset, $\beta = 0.25 \pm 0.03$ mJ/K, attributable to weak substrate heterogeneity. Inset shows heat capacity data from which these results are obtained, and includes two coverages close to layer promotion at $6.3 \pm 0.2$ nm$^{-2}$, where L2 starts to form. The distinctive heat capacity maximum at $T_0$ is driven toward $T = 0$ with increasing coverage. Fits to heat capacity data are shown in the inset: fits to low-temperature data for $T < T_0$ (LT, dashed line); fits to data at all temperatures (extended, solid line). For details, see text and supporting online material. (**B**) Total sample magnetization inferred from continuous-wave NMR at selected coverages. Data at 8.00, 8.50, and 9.00 nm$^{-2}$ show a clear maximum near $T_0$. The Curie-law magnetization of local moments with a density of 6.30 nm$^{-2}$ and the magnetization of an ideal Fermi gas are shown for comparison. Below $T_0$, a coherent heavy-fermion liquid forms with weakly temperature-dependent (Pauli) susceptibility. The upturn at the lowest temperatures, which is coverage dependent, may arise from spins localized by substrate heterogeneity. The magnetization isotherm at 1.0 mK [inset of (B)] shows a rapid growth in $^3$He nuclear magnetization, starting at a coverage of 9.2 nm$^{-2}$. For reference, the main figure shows the temperature dependence of the magnetization at coverages of 9.25 and 9.85 nm$^{-2}$.

maximum close to the characteristic temperature $T_0$. At higher temperatures, data from all coverages converge toward the Curie-law magnetization of a film with a density of 6.3 nm$^{-2}$, corresponding to the density of layer L1 (*26*). This Curie contribution of L1 dominates $M$ relative to the Pauli magnetization of L2. Furthermore, at the highest temperatures, the values of $\gamma(T)$ correspond to an effective mass ratio of about 3. These magnetization and heat capacity data show that at $T > T_0$ (region B of phase diagram, Fig. 1), L1 and L2 are effectively decoupled into an Anderson lattice of almost localized fermions (L1) and a layer of weakly correlated itinerant fermions (L2). Thus, $T_0$ appears to play the role of the Kondo-lattice temperature (*27*).

This behavior of the $^3$He bilayer is consistent with the usual picture of heavy-fermion systems in which the high quasi-particle mass at low temperatures arises from the conversion of the spin entropy of the almost localized electronic moments (*28*). In the present case, the entropy arises from the nuclear spins of the $^3$He atoms in L1.

**Evidence for quantum criticality.** A plot of the inverse effective mass ratio against coverage (Fig. 3) is linear over the range of measurements, and it extrapolates to an apparent mass divergence at $n_c = 9.9 \pm 0.1$ nm$^{-2}$. The coverage dependence of $T_0$, read directly from the heat capacity data, is consistent with a power-law scaling toward this critical coverage, $T_0 \propto \delta^\alpha$, with $\delta = 1 - (n/n_c)$ and $\alpha = 1.7 \pm 0.1$. Because $T_0$ and $m/m^*$ both appear to vanish, by extrapolation, at the same coverage, we identify $n_c$ as an apparent QCP of the $^3$He fluid bilayer system.

The "pseudogap" $\Delta$ also decreases approaching $n_c$. However, the inferred $\Delta$ depends strongly on the fit procedure adopted (Fig. 3 and supporting online material). This prevents us from drawing robust conclusions on its scaling near the putative QCP.

**Near the QCP: Intervening phase.** As the $^3$He coverage is increased toward $n_c$, the putative QCP is preempted by an "intervening phase" at $n_I = 9.2$ nm$^{-2}$ (region C of phase diagram, Fig. 1). The lower bound of this phase is clearly marked by the sharp increase in the low-temperature magnetization isotherm, taken at 1 mK (Fig. 2B, inset). There is no clear signature of $n_c$ in the magnetization data. However, heat capacity data for coverages in the range 9.2 to 9.85 nm$^{-2}$ (Fig. 4) show a secondary maximum at higher temperatures, in addition to a low-temperature heat capacity peak. The temperature of this feature decreases toward zero, approximately linearly with coverage (Fig. 4, inset). It vanishes, by linear extrapolation, at 9.95 ± 0.05 nm$^{-2}$, thus marking the upper bound of the intervening phase. This coverage coincides with $n_c$, the QCP inferred previously from the extrapolation of $m/m^*$. We suggest that the intervening phase is a hole-doped Mott insulator.

**Selective Mott transition of L1: Decoupled layers.** At coverages above the QCP at 9.9 nm$^{-2}$ (at which the density of L2 is 3.6 nm$^{-2}$), a uniform local-moment Mott insulator phase of L1 is found (region D of phase diagram, Fig. 1). Over the coverage range from 9.85 to 12.0 nm$^{-2}$, data from detailed measurements of the heat capacity and magnetization (figs. S2 and S3) are fit by the sum of two independent contributions: a localized solid (L1) and a 2D Fermi fluid (L2), in the same way as previous data on magnetism of the second layer of pure $^3$He films have been treated. The heat capacity still exhibits a maximum at $T \sim J_c$, which now arises from short-range magnetic order in the 2D frustrated magnet L1. The effective exchange constant inferred from the heat capacity, $J_c$, decreases over the same coverage range from 6.5 to 4.5 mK, whereas the density of L1 remains constant at 6.3 ± 0.1 nm$^{-2}$. This density is consistent with the formation of a 13/19 triangular superlattice (*29*) with respect to the underlying $^4$He layer, which has a density of 9.2 nm$^{-2}$. At 9.85 and 12.0 nm$^{-2}$, the magnetization at 1 mK corresponds to $0.3M_{sat}$ and $0.7M_{sat}$, respectively (Fig. 2B, inset), where $M_{sat}$ is the saturation magnetization of L1. The nature of the magnetic ground state of this frustrated 2D magnet is not understood. The effective mass ratio of the Fermi liquid L2, inferred from fits to the heat capacity, increases modestly from 2.7 to 3.1 over this coverage range, whereas its magnetic degeneracy temperature $T_F^{**}$ inferred from magnetization data (*26*) is about 500 mK.

We conclude that at $n > n_c$ the bilayer comprises a 2D frustrated magnet (L1) and an

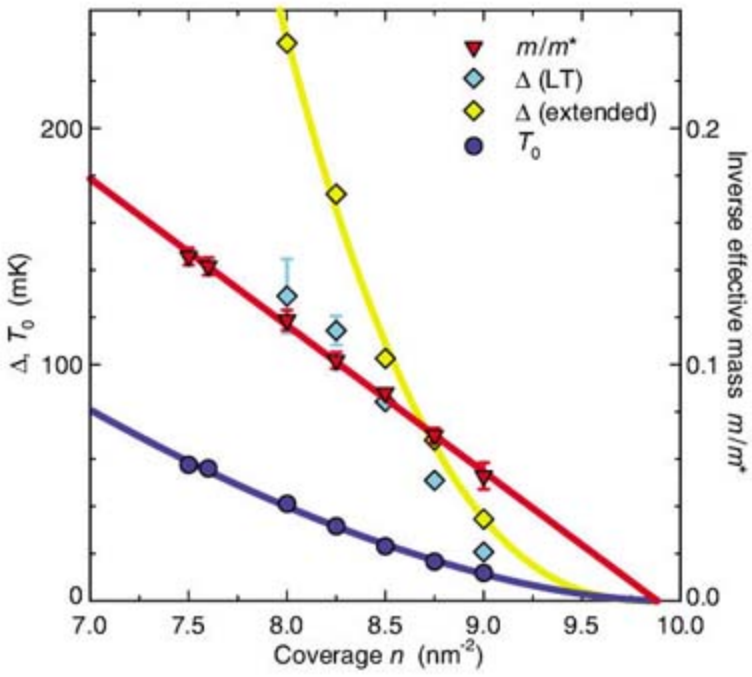



**Fig. 3.** Critical behavior inferred from heat capacity data. The effective mass, determined from $\gamma(T)$ at $T << T_0$, shows an apparent divergence at critical coverage $n_c = 9.9 \pm 0.1$ nm$^{-2}$ obtained from a linear extrapolation of $m/m^*$. The coverage dependence of $T_0$ is consistent with a power-law scaling toward this critical coverage, $T_0 \propto \delta^\alpha$, with $\delta = 1 - n/n_c$ and $\alpha = 1.7 \pm 0.1$, where the error in the exponent reflects the uncertainty in the critical coverage. The inferred "pseudogap" $\Delta$ is very sensitive to the fit procedure. Fits to low-temperature data for $T < T_0$ (LT, blue diamonds) suggest a collapse to zero near 9.2 nm$^{-2}$; extended fits over the entire temperature range are consistent with $\Delta \propto \delta^\sigma$ and $\sigma = 2.5 \pm 0.2$.

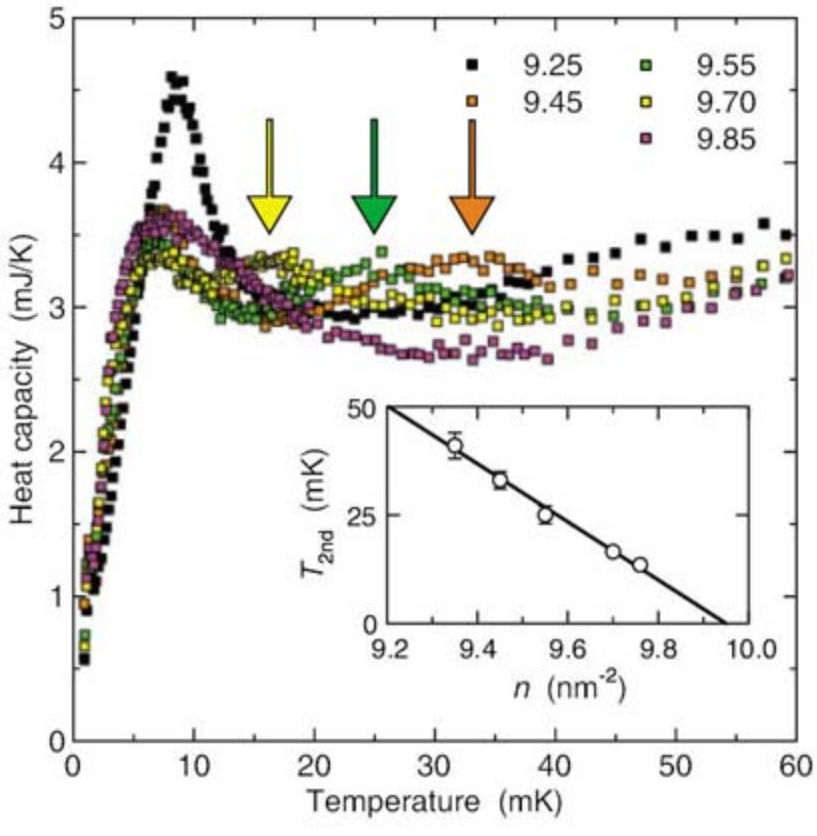



**Fig. 4.** Heat capacity data in the intervening phase. Starting at a coverage of 9.25 nm$^{-2}$, the heat capacity exhibits a broad secondary maximum at higher temperature. As shown in the inset, the temperature of this secondary maximum linearly extrapolates to zero at a coverage near $n_c = 9.9$ nm$^{-2}$.

itinerant fluid overlayer L2. Effective mass renormalization due to critical fluctuations, expected at $n > n_c$ and arising from coupling between the mobile quasi-particles in L2 and magnetic fluctuations in L1, should be manifest in the temperature range $T < J_c$ but is beyond our current experimental resolution.

**Discussion.** Returning to the new heavy-fermion phase (region A), we interpret the apparent mass divergence approaching the QCP at $n_c$ as a "bandwidth-controlled" Mott-Hubbard transition (*30*) of L1, driven by varying the density of the overlayer L2, with only small changes in the density of L1. The maximum in $\gamma(T)$, observed here in bilayer $^3$He and not seen in the density-driven Mott transition in a fluid monolayer (*15*), is evidence for the importance of interlayer interactions.

The natural model for the $^3$He bilayer is the periodic Anderson model (PAM) of two hybridized bands (*31*). This model features a sharp peak in the quasi-particle energy density of states at the Fermi energy, giving rise to a large mass renormalization, and a "pseudogap" (*27*, *32*). The parameters of this Hamiltonian, in particular the bare dispersion in L1, the correlations in L1 (modeled by an effective on-site repulsion), and the hybridization interaction (Kondo-like exchange of particles between L1 and L2), are all $^3$He coverage dependent. In the framework of the PAM, the layer L1, whose density we find remains approximately constant, corresponds to a narrow band close to half-filling. Increasing the total coverage increases the density of L2, which has a relatively wide bare bandwidth. The density of L2 should tune the correlations and bare bandwidth of L1, as well as the hybridization interaction.

The physical mechanisms can be pictured as follows. The effective hard-core repulsion felt by L1 atoms due to L2 restricts their zero-point motion normal to the surface, and gives rise to a reduction of the bare bandwidth within L1. Equivalently, the van der Waals attraction between the atoms in L2 and the composite substrate creates an effective pressure proportional to the density of L2, which eventually causes L1 to solidify. The hybridization can be thought of in terms of "valence fluctuations" in L1, the creation of a virtual particle-vacancy pair: A particle in L1 jumps into L2, leaving a vacancy in L1, and this vacancy is filled by another particle from L2. It is expected that this process will depend strongly on the density of L2 (*33*, *34*), a result that may be tested theoretically by path integral Monte Carlo calculations.

**Concluding remarks.** We have identified a new model system for studying the competing physics of local-moment formation and Kondo coupling, to compare against the behavior of f-electron QCPs. Our key result is that the characteristic energy scale $T_0$, arising from Kondo-like interlayer coupling, vanishes, by power-law extrapolation, at the same coverage $n_c$ (QCP) at which the effective mass appears to diverge, corresponding to the vanishing of the distinct energy scale $T_F^*$ (Fermi temperature). This appears to be an example of local quantum criticality (*35*), and is in contrast to the usual application of conventional theory to heavy-fermion systems (*1*), which assumes a finite Kondo-lattice scale at the QCP. Consistent with this picture, we find that at higher coverages, above $n_c$, the uniform local-moment phase of L1 and the fluid overlayer L2 are decoupled.

A number of unresolved questions remain concerning the detailed behavior in the vicinity of the QCP. The approach to the QCP at $n_c$, identified by extrapolation of $T_0$ and $m/m^*$, is interrupted by a sharp increase in magnetization at $n_1$. This has recently been discussed, in terms of the Kondo-breakdown QCP scenario, as evidence for a QCP at $n_1$ (*36*). We note that a collapse of the "pseudogap" scale at $n_1$ is consistent with the data, and that this onset of the intervening phase coincides with the crossover in the two energy scales $T_0$ and $J_c$. Clarification will require a more detailed investigation of thermodynamic quantities close to this coverage, as well as studies of the spin dynamics close to the putative QCP.

$^3$He is an intrinsically isotropic, neutral Fermi system in which the quasi-particle effective mass directly reflects the fermionic correlations, the spin-orbit interaction is negligible, and crystal-field interactions are absent. Mapping the bilayer system onto the various candidate models for quantum criticality remains a future theoretical challenge. The emergence of the rich behavior from the $^3$He bilayer system—a variant of the Fermi-liquid paradigm, liquid $^3$He, with reasonably well-established "bare parameters"—may contribute to an improved understanding of the far more complex heavy-fermion intermetallics, such as $YbRh_2Si_2$ (*37*, *38*).

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21. The bare substrate used in this work is a sample of exfoliated graphite with a total surface area of 182 m$^2$. $^4$He has a higher binding energy to the graphite surface than does $^3$He, arising from its smaller zero-point energy. This preferential adsorption is exploited to preplate the surface. The $^4$He coverage required for precisely two atomic layers is 21.2 nm$^{-2}$, as shown by previous work (*39*).
22. See supporting material on *Science* Online.
23. The effective mass $m^*$ is deduced via the relation $\gamma = \pi k_B^2 A m^*/3\hbar^2$, where $h$ is Planck's constant, $k_B$ is Boltzmann's constant, and $A$ is the total substrate area of 182 m$^2$. The Fermi temperature is given by $T_F^* = 0.505 n/(m^*/m)$ (K nm$^2$).
24. The highest value of $T_0$ observed in the fluid bilayer phase, 58 mK at 7.5 nm$^{-2}$, is an order of magnitude greater than the value of the effective exchange interaction $J_c$ in the solid phase of L1, $J_c = 6.5$ mK at $n = 9.9$ nm$^{-2}$, when the uniform solid first forms.
25. The area under the NMR line is numerically integrated to infer the $^3$He nuclear magnetization. NMR selectively and directly measures the $^3$He magnetization, $M$, in the applied static field. The Curie constant has been determined in a separate experiment in the same sample chamber on a paramagnetic $^3$He monolayer adsorbed on bare graphite.
26. For a strongly correlated 2D $^3$He fluid monolayer, previous work (*12*) has shown that the crossover from Curie-law susceptibility at high temperatures to a Pauli susceptibility in the degenerate regime is well described by $\chi = C/(T^2 + T_F^{**2})^{1/2}$, with Curie constant $C$, and an effective degeneracy temperature $T_F^{**} = T_F^0(1 + F_0^a)/(m^*/m)$, where $T_F^0 = 0.505n$ (K nm$^2$) is the Fermi temperature of the corresponding ideal Fermi gas and $F_0^a$ is a Fermi liquid Landau parameter. However, in the $^3$He bilayer system we find that the onset of spin degeneracy is governed by $T_0$ rather than $T_F^{**}$. For example, at 9.0 nm$^{-2}$, $T_F^{**} = 60$ mK (using the parameters of the heavy-fermion state at $T << T_0$), while $T_0 = 12$ mK.
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### Supporting Online Material

www.sciencemag.org/cgi/content/full/1143607/DC1
Materials and Methods
Figs. S1 to S8
Tables 1 and 2
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# Humans Have Evolved Specialized Skills of Social Cognition: The Cultural Intelligence Hypothesis

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Humans have many cognitive skills not possessed by their nearest primate relatives. The cultural intelligence hypothesis argues that this is mainly due to a species-specific set of social-cognitive skills, emerging early in ontogeny, for participating and exchanging knowledge in cultural groups. We tested this hypothesis by giving a comprehensive battery of cognitive tests to large numbers of two of humans' closest primate relatives, chimpanzees and orangutans, as well as to 2.5-year-old human children before literacy and schooling. Supporting the cultural intelligence hypothesis and contradicting the hypothesis that humans simply have more "general intelligence," we found that the children and chimpanzees had very similar cognitive skills for dealing with the physical world but that the children had more sophisticated cognitive skills than either of the ape species for dealing with the social world.

Humans have brains roughly three times larger than those of their nearest primate relatives, the great apes (*1*, *2*), and of course have many cognitive skills not possessed by other primates as well, from language to symbolic mathematics to scientific reasoning. The questions from an evolutionary point of view—especially given the enormous energetic expense of a large brain (*3*)—are how and why humans have evolved such powerful and distinctive cognitive abilities requiring so much neural tissue.

One hypothesis is the general intelligence hypothesis. Larger brains enable humans to perform all kinds of cognitive operations more efficiently than other species: greater memory, faster learning, faster perceptual processing, more robust inferences, longer-range planning, and so on. The alternative is the adapted intelligence hypothesis (*4*). Cognitive abilities evolve in response to relatively specific environmental challenges, and so we may see caching birds with exceptional memory skills, homing pigeons with marked skills of spatial navigation, bees with complex systems of communication, and so forth (*5*). In the case of primates, some theorists have proposed that the distinctive aspects of primate cognition evolved mainly in response to the especially challenging demands of foraging for seasonal fruits and resources embedded in substrates [the ecological intelligence hypothesis (*6*, *7*)], whereas others have proposed that the distinctive aspects of primate cognition evolved mainly in response to the especially challenging demands of a complex social life of constant competition and cooperation with others in the social group [the social intelligence hypothesis (*8*–*11*)].

In the case of humans, one reasonable hypothesis involves extending the primate social intelligence hypothesis to reflect the fact that humans are not just social but "ultra-social" (*12*). That is, whereas primates in general have evolved sophisticated social-cognitive skills for competing and cooperating with conspecifics, humans have also evolved skills that enable them to actually create different cultural groups, each operating with a distinctive set of artifacts, symbols, and social practices and institutions. To function effectively in the cultural world into which they are born, human children simply must learn to use these artifacts and tools and to participate in these practices, which require some special social-cognitive skills of social learning, communication, and "theory of mind" (*13*). Some other ape species transmit some behaviors socially or culturally (*14*, *15*), but their species-typical cognition does not depend on participating in cultural interactions in the same way as it does in humans, who must (i) learn their native language in social interactions with others, (ii) acquire necessary subsistence skills by participating with experts in established cultural practices, and (iii) (in many cultures) acquire skills with written language and mathematical symbols through formal schooling (*16*). In the end, human adults will have all kinds of cognitive skills not possessed by other primates, but this outcome will be due largely to children's early emerging, specialized skills for absorbing the accumulated skillful practices and knowledge of their social group (so that a child growing up outside of any human culture would develop few distinctively human cognitive skills). Humans' especially powerful skills of social-cultural cognition early in ontogeny thus serve as a kind of "bootstrap" for the distinctively complex development of human cognition in general. We may call this the cultural intelligence hypothesis.

There have been no direct tests of the cultural intelligence hypothesis, nor any direct comparisons of it with other hypotheses of human cognitive evolution. The social intelligence hypothesis for primates in general is supported by positive correlations between relative brain size (i.e., neocortex size) and social variables such as group size or grooming clique size [as an index of social complexity (*11*, *17*–*20*)]. This evidence provides support for the general social direction of the cultural intelligence hypothesis, but overall correlations do not tell us the basis of the brain size differences in terms of particular cognitive skills, nor do they help us to identify which cognitive skills humans may have that other primates lack. There have also been some experimental studies that directly compared the performance of several primate species on a few cognitive tasks, but in the only meta-analysis of those studies, none of the tasks targeted social cognition and humans were not represented (*21*). Several other experimental studies have directly compared some individual cognitive skills of humans (mostly children) and nonhuman primates (mostly apes), but each of these studies has been conducted with different individuals, and indeed the ages of the children and the members of the nonhuman primate species are inconsistent across studies (*22*).

What is needed to test the cultural intelligence hypothesis is a systematic comparison of a representative range of cognitive skills among a single set of human and nonhuman primate individuals, which has so far not been done. In such a comparison, the cultural intelligence hypothesis predicts that there should be an age in early human ontogeny (specifically, an age before children have been seriously influenced by written language, symbolic mathematics, and formal education) at which humans' skills of physical cognition (concerning things such as space, quantities, and causality) are very similar to those of our nearest primate relatives but at which their skills of social-cultural cognition (specifically those most directly involved in cultural creation and learning, such as social learning, communication, and theory of mind) are already distinctively human. This is in stark contrast to the general intelligence hypothesis, which predicts that human cognition should differ from that of other primates uniformly, with no difference between physical and social cognition.

In the current study, therefore, we sought to identify any distinctive features of human cognition that may exist at an early stage of ontogeny and, in this way, to assess and directly compare the cultural intelligence and general intelligence hypotheses of human cognitive evolution. We did this by administering a comprehensive battery of cognitive tests to a large number of chimpanzees (*Pan troglodytes*) (one of humans' two closest living relatives), orangutans (*Pongo pygmaeus*) (a more distantly related great ape), and human children (*Homo sapiens*) at 2.5 years of age. Of crucial importance to our analysis were

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the following: (i) all subjects from all three species were naïve to the tests from the test battery; (ii) the apes lived in rich, semi-natural environments; and (iii) there was a sufficient number of subjects to properly test, as virtually no previous studies have done, the role of gender, age, and temperament (measured in a separate test) as possible mediators of cognitive performance on the tasks.

**Methods: the test battery and its administration.** The Primate Cognition Test Battery (PCTB) was constructed based on the theoretical analysis of primate cognition by Tomasello and Call (*22*). In this analysis, the primary division is between physical cognition and social cognition. Although primates in their natural habitats regularly use skills of physical and social cognition together [e.g., foraging for food while competing with groupmates (*23*, *24*)], in theory the two sets of skills are distinct because physical cognition deals with inanimate objects and their spatial-temporal-causal relations, whereas social cognition deals with other animate beings and their intentional actions, perceptions, and knowledge.

More specifically, in this analysis, primate cognition of the physical world evolved mainly in the context of foraging: To locate food, primates need cognitive skills for dealing with "space"; to choose wisely among multiple food sources, they need cognitive skills for dealing with "quantities"; and for extracting food from difficult places, they need cognitive skills for understanding "causality" (including, for some species, the context of tool use). In this analysis, primate social cognition evolved because of the tension between cooperation and competition among group members: To manipulate the behavior of others, primates need skills of "communication"; to learn things vicariously from observing others, they need skills of "social learning"; and to predict the behavior of others in competition, they need cognitive skills for understanding psychological states such as goals and perceptions ("theory of mind"). The PCTB therefore comprised the two domains of physical cognition and social cognition, each of which comprised three cognitive scales (the six terms enclosed in quotes above), with each scale being constructed with one or more specific tasks composed of several items each. Most of the items were derived from previously published studies of primate cognition (table S2), whereas others were created for the PCTB and validated before use with the chimpanzees and orangutans at the Wolfgang Köhler Primate Research Center in Leipzig, Germany. Table 1 briefly summarizes the structure of PCTB (*25*) (movies S1 to S32).

The PCTB was administered to three groups of participants. First were 106 chimpanzees (53 males and 53 females; 3 to 21 years of age; mean age: 10 years) that lived either at the Ngamba Island chimpanzee sanctuary, Lake Victoria, Uganda, or at the Tchimpounga chimpanzee sanctuary, Republic of Congo. Second were 32 orangutans (17 males and 15 females; 3 to 10 years of age; mean age: 6 years) that lived at the Orangutan Care Center and Quarantine in Pasir Panjang, Kalimantan, Indonesia. All of these apes live in the richest social and physical environments available to captive apes and have grown up in close contact with humans who feed and care for them. Third were 105 human children [52 males and 53 females; 2.5 years of age (±2 months)] from a medium-sized city in Germany. All children had been using language for ~1 year (*25*) (table S1).

Participants were individually tested by a human experimenter, with the same experimenter testing a subject throughout the entire battery. Each participant completed all tasks in the PCTB, which took from 3 to 5 hours altogether, generally in the same order across several days of testing (table S3). The human children were

**Table 1.** The PCTB, including domains, scales, and tasks (*25*).

| Domain | Scale | Task | Description |
|---|---|---|---|
| Physical | Space | Spatial memory (1 item, 3 trials) | Locating a reward. |
| | | Object permanence (3 items, 9 trials) | Tracking of a reward after invisible displacement. |
| | | Rotation (3 items, 9 trials) | Tracking of a reward after a rotation manipulation. |
| | | Transposition (3 items, 9 trials) | Tracking of a reward after location changes. |
| | Quantities | Relative numbers (1 item, 13 trials) | Discriminating quantity. |
| | | Addition numbers (1 item, 7 trials) | Discriminating quantity with added quantities. |
| | Causality | Noise (2 items, 6 trials) | Causal understanding of produced noise by hidden rewards. |
| | | Shape (2 items, 6 trials) | Causal understanding of appearance change by hidden rewards. |
| | | Tool use (1 item, 1 trial) | Using a stick in order to retrieve a reward which is out of reach. |
| | | Tool properties (5 items, 15 trials) | Understanding of functional and nonfunctional tool properties. |
| Social | Social learning | Social learning (3 items, 3 trials) | Solving a simple but not obvious problem by observing a demonstrated solution. |
| | Communication | Comprehension (3 items, 9 trials) | Understanding communicative cues indicating a reward's hidden location. |
| | | Pointing cups (1 item, 4 trials) | Producing communicative gestures in order to retrieve a hidden reward. |
| | | Attentional state (4 items, 4 trials) | Choosing communicative gestures considering the attentional state of the recipient. |
| | Theory of mind | Gaze following (3 items, 9 trials) | Following an actor's gaze direction to a target. |
| | | Intentions (2 items, 6 trials) | Understanding what an actor intended to do (unsuccessfully). |

tested on 5 days within a 2-week period, and the apes were tested on consecutive days, averaging a total of 8 days. Chimpanzees and orangutans were tested in a familiar room, and human children were tested in a child laboratory and accompanied by a parent who was told not to influence or help in any way. To measure the comfort level of participants in the test situation (because this could be a mediator of their performance in the PCTB), we also gave subjects (within the first 4 days of testing) a temperament test designed to assess their reaction to novel objects, people, and rewards (*25*) (tables S6 and S7). All testing was videotaped.

For most of the tasks, a human experimenter (E1) sat behind a table facing the subject through a Plexiglas window (children and some apes) or a mesh panel (apes only). The window had three holes at different positions, through which subjects could insert a finger to indicate their choice when necessary (figs. S1 and S2). On all trials, E1 always waited until the subject was facing her before beginning a trial. For trials requiring a choice, the position of the reward was counterbalanced across either two or three locations (depending on the task) but the reward was never hidden for more than two consecutive trials in the same place. In a few tasks, subjects were tested in other setups, requiring them to do such things as to use a simple tool, follow gaze direction, or gesture to E1 (*25*).

Subjects' responses were initially coded live by E1 except for gaze-following trials, which E1 coded from videotape after the test. A second observer independently scored (from videotape) 100% of the trials for human children and chimpanzees and 20% of the trials for orangutans. The inter-observer agreement for all tasks combined was 98% for orangutans, 99% for chimpanzees, and 99% for human children (table S4).

**Results.** Figure 1 presents the results at the most general level of analysis. Averaging across all of the tasks in the physical domain, humans and chimpanzees were correct on ~68% of the trials, whereas orangutans were correct on ~59% of the trials (the absolute values are not especially meaningful because some tasks had a 50 or 33% chance of success by guessing, and some tasks had no possibility for guessing). Statistically, the humans and chimpanzees did not differ from one another in the physical domain, but they were both more skillful than the orangutans ($P < 0.001$ in both cases). In the social domain, a very different pattern emerged. Averaging across all of the tasks in the social domain, the human children were correct on ~74% of the trials, whereas the two ape species were correct about half as often (33 to 36% of the trials). Statistically, the humans were more skillful than either of the two ape species ($P < 0.001$ in both cases), which did not differ from one another.

Figure 2 presents the results at the level of the six scales. In the physical domain, there were no differences among species on the quantities scale. On both the space and causality scales, however, humans and chimpanzees did not differ from one another, but both were more skillful than orangutans ($P < 0.001$ in all cases). The difference between chimpanzees and orangutans remained even after controlling for age (*25*). In the social domain, the pattern was again different from the physical domain and the same for all three of the scales. Human children were more skillful than either of the ape species in each of the three social scales ($P < 0.001$ in all cases), and the apes did not differ from one another.

Table 2 lists species' performance on the 16 different tasks within each of the scales (note that social learning is a scale and a task). The overall pattern is that within the physical domain, human children and chimpanzees each were better at some tasks than the other, with orangutans often representing an outlier. Within the four spatial tasks, children were better than chimpanzees at one task (object permanence), whereas the chimpanzees outperformed the children at another task (transposition). In terms of quantities, all three species were similar at judging which of two quantities is larger, but chimpanzees were better than both of the other species at combining quantities in order to make a judgment. Children were better than both ape species at the three causality tasks in which a judgment must be made before manipulation or choice, whereas chimpanzees were better than children and orangutans at the one causality task involving active tool use. Within the social domain, again the pattern was very different. As predicted, the human children were consistently more skillful than both of the ape species (at five

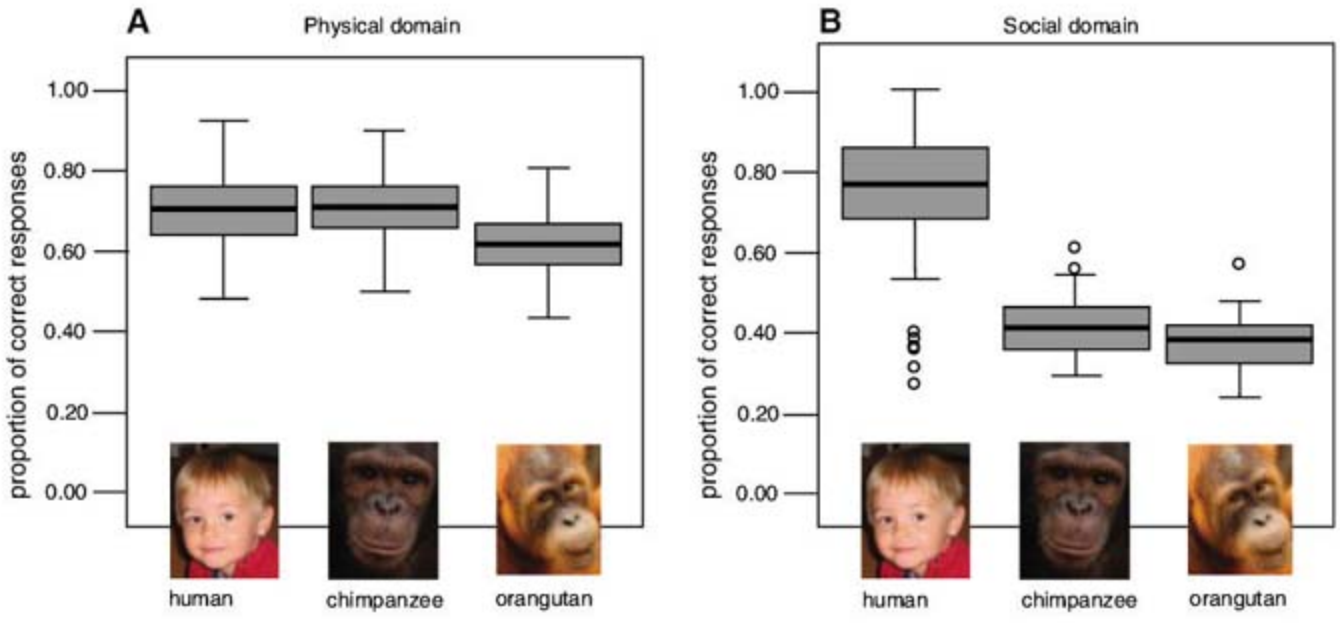


**Fig. 1.** Physical domain (**A**) and social domain (**B**). The box plots show the full distribution of the proportion of correct responses for physical and social domains of the PCTB for each species: median, quartiles, and extreme values. Boxes represent the interquartile range that contains 50% of values (range from the 25th to the 75th percentile). The line across the box indicates the median. The whiskers represent maximum and minimum values, excluding outliers [indicated by circles, at least 1.5 times the interquartile range (i.e., 1.5 box lengths from the upper or lower edge of the box)] and extremes [indicated by asterisks, at least 3 times the interquartile range (i.e., >3 box lengths from the edge)]. Statistical comparisons on each domain were made by multivariate analysis of variance (MANOVA), followed by analysis of variance (ANOVA) tests for each domain. Post-hoc tests (the Bonferroni correction was used when the equality of variances assumption holds, and the Dunnett t3 correction was used otherwise) followed in case a significant effect was detected. Performance on the PCTB as a whole differed significantly across species (MANOVA with species and gender as between-subject factors and performance in both domains of the PCTB as the dependent variables; Wilk's Lambda: $F_{4,472} = 123.965$, $P < 0.001$, $\eta^2 = 0.51$). No statistically significant differences were detected between genders, but there was an interaction between species and gender (Wilk's Lambda: $F_{4,472} = 2.815$, $P < 0.025$, $\eta^2 = 0.02$). Univariate analyses (ANOVA) showed that the differences across species were significant for both domains: physical ($F_{2,237} = 19.921$, $P < 0.001$, $\eta^2 = 0.14$) and social ($F_{2,237} = 311.224$, $P < 0.001$, $\eta^2 = 0.72$). Univariate analyses for the interaction between species and gender revealed that there was a significant interaction for the physical domain ($F_{2,237} = 5.451$, $P = 0.005$, $\eta^2 = 0.04$) but not for the social domain ($F_{2,237} = 0.224$, $P = 0.799$). Post-hoc tests (Dunnett t3 correction) revealed that humans and chimpanzees performed better than orangutans in the physical domain (for both $P < 0.001$, with no difference between humans and chimpanzees). However, post-hoc tests (Dunnett t3 correction) showed that human children outperformed both chimpanzees and orangutans in the social domain (both $P < 0.001$). Post-hoc tests for the interaction between species and gender in the physical domain showed that female children were better than male children ($P = 0.001$). No other gender differences were found.

out of six tasks), and the two apes did not differ from one another on any task.

To test for possible species differences in individual variability, we computed a coefficient of variation and a 95% two-sided exact confidence interval for both domains for each of the three species (table S5). There were no significant species differences in variability. For two of the three species (humans and chimpanzees), there was more individual variability in the social than in the physical domain (the trend for orangutans was in the same direction but not significantly so), but this may be due to the larger proportion of tasks with the possibility of chance success in the physical domain (90% in the physical domain and 33% in the social domain), which provides a higher baseline for unskillful individuals (*25*).

There was no effect of gender for any of the species on any of the social scales. On the physical scales, chimpanzee males outperformed chimpanzee females on the scale space, whereas human females outperformed human males on the scale quantities. Human females also outperformed human males at the level of the physical domain as a whole (although this was not so for the two ape species).

In terms of temperament (operationalized as approach behavior to novel objects, people, and rewards), the human children were shyer or less interested in the novel items in the test situation than were the two ape species, which were bolder or more interested ($P < 0.001$ in both cases) [(*25*) and tables S6 and S7]. Also, children's temperament measures did not correlate with any aspect of their cognitive performance. For the two ape species, there was also no correlation of temperament with any of the social scales, but ape individuals that approached novel situations more quickly (i.e., were bolder and more in-

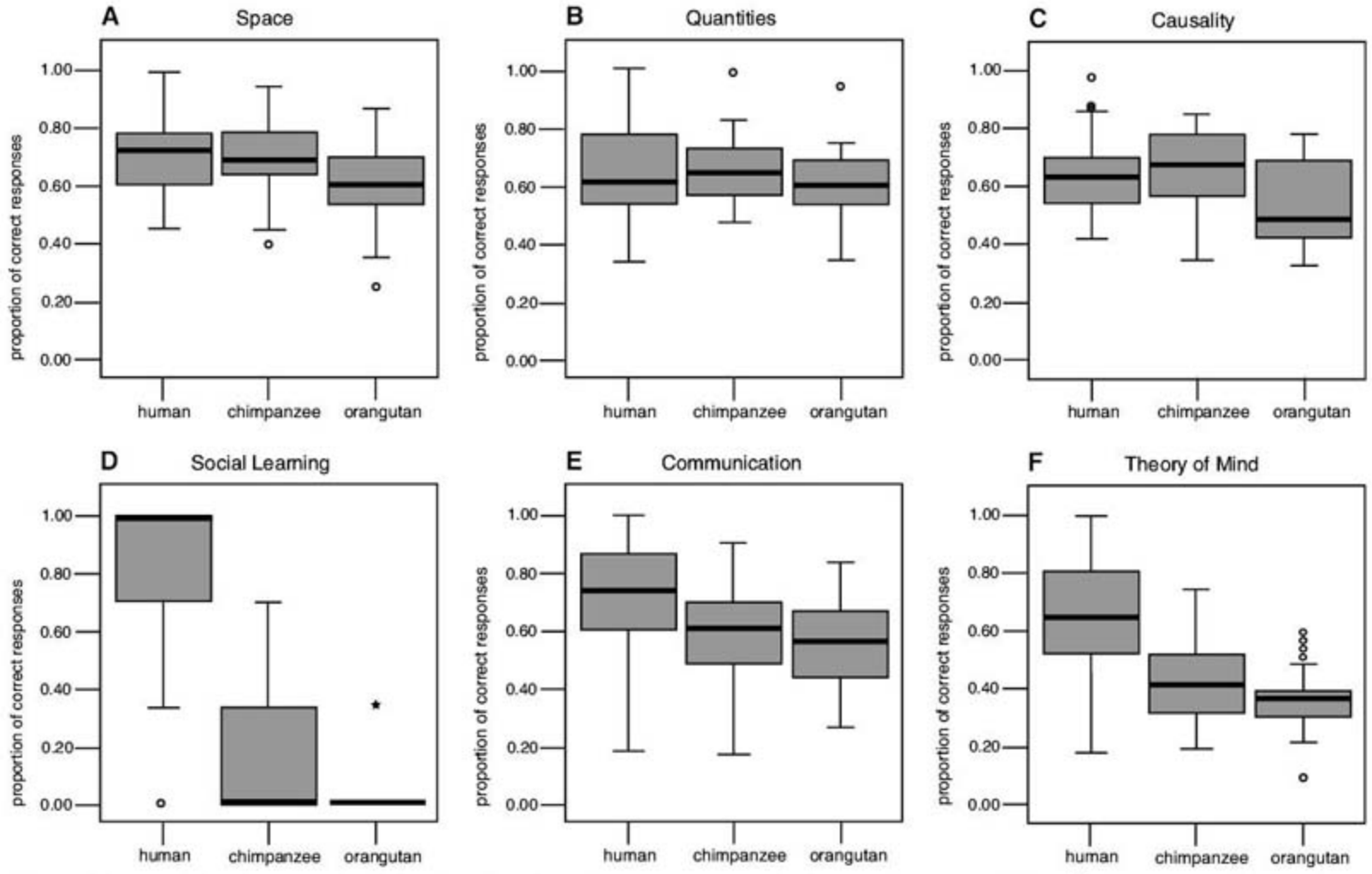


**Fig. 2.** Space (**A**), quantities (**B**), causality (**C**), social learning (**D**), communication (**E**), and theory of mind (**F**). The box plots show the full distribution of the proportion of correct responses on the six scales of the PCTB for each species: median, quartiles, and extreme values. Boxes, lines, whiskers, outliers, and extremes are as described in Fig. 1. Statistical comparisons on each scale were made by MANOVA, followed by ANOVAs for each scale. Post-hoc tests (the Bonferroni correction was used when the equality of variances assumption holds, and the Dunnett t3 correction was used otherwise) followed in case a significant effect was detected. Performance in the physical domain differed significantly across species (MANOVA with species and gender as between-subject factors and performance in the three scales of the physical domain as the dependent variables; Wilk's Lambda: $F_{6,470} = 6.934$, $P < 0.001$, $\eta^2 = 0.08$). No statistically significant differences were detected between genders. However, there was a significant interaction between species and gender (Wilk's Lambda: $F_{6,470} = 2.393$, $P = 0.027$, $\eta^2 = 0.03$). Univariate analyses (ANOVA) showed that the differences across species were significant for the scales space ($F_{2,237} = 11.033$, $P < 0.001$, $\eta^2 = 0.09$) and causality ($F_{2,237} = 8.617$, $P < 0.001$, $\eta^2 = 0.07$). No species difference was found for the scale quantities ($F_{2,237} = 1.970$, $P = 0.142$). Univariate analyses for the interaction between species and gender revealed that there was a significant interaction for the scales space ($F_{2,237} = 4.095$, $P = 0.018$, $\eta^2 = 0.03$) and quantities ($F_{2,237} = 3.147$, $P = 0.045$, $\eta^2 = 0.03$) but not for causality ($F_{2,237} = 0.199$, $P = 0.820$). Post-hoc tests (Bonferroni correction) revealed that humans and chimpanzees performed better than orangutans in the scales of space and causality (for all $P < 0.001$), with no difference between chimpanzees and humans on these scales. Post-hoc tests for the interaction between species and gender for space showed that chimpanzee males outperformed females ($P = 0.047$). Post-hoc tests showed that human females outperformed males on the quantities scale ($P = 0.004$). No other gender differences were found. Performance in the social domain differed significantly across species (MANOVA with gender and species as between-subject factors and performance in the three scales of the social domain as the dependent variables; Wilk's Lambda: $F_{6,470} = 96.846$, $P < 0.001$, $\eta^2 = 0.55$). No statistically significant differences were detected between gender, and no significant gender-species interaction was found. Univariate analyses (ANOVA) showed that the differences across species were significant for the all three scales: social learning ($F_{2,237} = 382.145$, $P < 0.001$, $\eta^2 = 0.76$), communication ($F_{2,237} = 24.717$, $P < 0.001$, $\eta^2 = 0.17$), and theory of mind ($F_{2,237} = 70.646$, $P < 0.001$, $\eta^2 = 0.37$). Post-hoc tests (Dunnett t3 correction) revealed that humans outperformed chimpanzees ($P < 0.001$) and orangutans ($P < 0.001$) in social learning, communication, and theory of mind. The performance of chimpanzees and orangutans in all three scales did not differ.

**Table 2.** Proportion of correct responses on each of the tasks across species. Statistical comparisons on each scale were made by MANOVAs (with species and gender as between-subject factors and performance on the different tasks within each scale as dependent variables), followed by ANOVAs (with species and gender as between-subject factor) for each scale and task. Post-hoc tests (the Bonferroni correction was used when the equality of variances assumption holds, and the Dunnett t3 correction was used otherwise) followed in case a significant effect was detected. In case of important deviations of the model assumptions, a Kruskal-Wallis test with post-hoc Mann-Whitney *U* tests with the Bonferroni correction was performed. The tool-use task was analyzed separately with a chi-square analysis because it consisted only of one trial with a yes or no response. Space: Performance in the scale space differed significantly across species (MANOVA, Wilk's Lambda: $F_{8,468} = 11.273$, $P < 0.001$, $\eta^2 = 0.16$). No significant differences were detected between genders, and there was no significant interaction between species and gender. Univariate analyses (ANOVA) showed that the differences across species were significant for each spatial task: for spatial memory ($F_{2,237} = 3.329$, $P = 0.038$, $\eta^2 = 0.03$), object permanence ($F_{2,237} = 27.911$, $P < 0.001$, $\eta^2 = 0.19$), rotation ($F_{2,237} = 3.564$, $P < 0.030$, $\eta^2 = 0.03$), and transposition ($F_{2,237} = 14.038$, $P < 0.001$, $\eta^2 = 0.11$). There was a statistically significant effect for spatial memory, but post-hoc tests (Dunnett t3 correction) revealed no significant difference across the three species. Pair-wise comparisons (Bonferroni correction) for object permanence showed that humans performed better than chimpanzees ($P < 0.001$) and orangutans ($P < 0.001$). Chimpanzees performed significantly better than orangutans on the task rotation ($P = 0.028$). Post-hoc tests for transposition revealed that chimpanzees outperformed humans ($P < 0.001$) and orangutans ($P < 0.001$) [see (*25*) for age effect]. Quantities: Performance in the scale quantities differed significantly across species (MANOVA, Wilk's Lambda: $F_{4,472} = 3.994$, $P = 0.003$, $\eta^2 = 0.03$). No statistically significant difference between genders was detected, and there was no significant interaction between species and gender. Because the model assumptions for an ANOVA were not met for both tasks within the quantities scale, nonparametric tests were performed. Kruskal-Wallis one-way ANOVA showed that the differences across species were significant for addition numbers ($\chi^2_2 = 9.574$, $P = 0.008$) but not for relative numbers ($\chi^2_2 = 4.149$, $P = 0.126$). Post-hoc tests, with Mann-Whitney *U* tests for addition numbers, revealed that chimpanzees performed better than humans ($U = 4462.00$, $z = -2.556$, $P = 0.011$) and orangutans ($U = 1192.50$, $z = -2.638$, $P = 0.008$). The species difference in addition numbers between chimpanzees and orangutans remained even after controlling for age by matching the age of chimpanzees and orangutans and comparing the performance of these individuals ($U = 735.50$, $z = -2.540$, $P = 0.011$). Causality: Performance in the scale causality differed significantly across species (MANOVA, Wilk's Lambda: $F_{6,470} = 33.093$, $P < 0.001$, $\eta^2 = 0.30$). No statistically significant differences were detected between genders, and there was no significant interaction between species and gender. Univariate analyses (ANOVA) showed that the differences across species were significant for each causality task: for noise ($F_{2,237} = 74.163$, $P < 0.001$, $\eta^2 = 0.39$), shape ($F_{2,237} = 29.335$, $P < 0.001$, $\eta^2 = 0.20$), and tool properties ($F_{2,237} = 20.211$, $P < 0.001$, $\eta^2 = 0.15$). Post-hoc tests (Bonferroni correction) revealed that humans performed better than chimpanzees ($P < 0.001$) and orangutans ($P < 0.001$) on the noise task. The same difference was found for the shape task (chimpanzees, $P < 0.001$; orangutans, $P < 0.001$) and for tool properties (chimpanzees, $P < 0.001$; orangutans, $P = 0.003$). Performance in tool use was significantly different across species ($\chi^2_2 = 55.815$, $P < 0.001$). Pair-wise comparison revealed that chimpanzees outperformed humans (Fisher's exact test, $P < 0.001$) and orangutans (Fisher's exact test, $P < 0.001$). The species difference in tool use between chimpanzees and orangutans remained even after controlling for age by matching the age of chimpanzees and orangutans and comparing the performance of these individuals (Fisher's exact test, $P = 0.018$). Social Learning: The social-learning scale was analyzed with a Kruskal-Wallis one-way ANOVA. A significant difference between species was found ($\chi^2_2 = 183.301$, $P < 0.001$). Post-hoc tests, with Mann-Whitney *U* tests, revealed that humans performed better than chimpanzees ($U = 255.00$, $z = -12.593$, $P < 0.001$) and orangutans ($U = 56.50$, $z = -8.935$, $P < 0.001$), which did not differ from one another. Communication: Performance in the communication scale differed significantly across species (MANOVA, Wilk's Lambda: $F_{6,470} = 24.462$, $P < 0.001$, $\eta^2 = 0.24$). No statistically significant differences were detected between genders, and there was no interaction between species and gender. Univariate analyses (ANOVA) showed that the differences across species were significant for the comprehension ($F_{2,237} = 67.021$, $P < 0.001$, $\eta^2 = 0.36$) and attentional-state tasks ($F_{2,237} = 19.155$, $P < 0.001$, $\eta^2 = 0.14$). However, there were no species differences in the pointing-cups task ($F_{2,237} = 0.087$, $P = 0.916$). Post-hoc tests (Bonferroni correction) revealed that humans performed better than chimpanzees ($P < 0.001$) and orangutans ($P < 0.001$) on the comprehension task. The same difference was found in the attentional-state task (chimpanzees, $P < 0.001$; orangutans, $P < 0.001$). Theory of mind: Performance in the theory-of-mind scale differed significantly across species (MANOVA, Wilk's Lambda: $F_{4,472} = 44.868$, $P < 0.001$, $\eta^2 = 0.28$) No statistically significant differences were detected between genders, and there was no interaction between species and gender. Univariate analyses (ANOVA) showed that the differences across species were significant for both the gaze-following task ($F_{2,237} = 23.096$, $P < 0.001$, $\eta^2 = 0.16$) and the intentions task ($F_{2,237} = 87.129$, $P < 0.001$, $\eta^2 = 0.42$). Post-hoc tests (Bonferroni correction) revealed that humans performed better than chimpanzees ($P < 0.001$) and orangutans ($P < 0.001$) on the gaze-following task. The same difference was found for the intentions task (chimpanzees, $P < 0.001$; orangutans, $P < 0.001$).

| | Human | Chimpanzee | Orangutan |
|---|---|---|---|
| Physical | $0.68^{O}$ | $0.68^{O}$ | 0.59 |
| Space | $0.71^{O}$ | $0.71^{O}$ | 0.60 |
| Spatial memory | 0.91 | 0.95 | 0.85 |
| Object permanence | $0.79^{C,O}$ | 0.64 | 0.60 |
| Rotation | 0.55 | $0.56^{O}$ | 0.46 |
| Transposition | 0.57 | $0.70^{H,O}$ | 0.47 |
| Quantities | 0.67 | 0.68 | 0.63 |
| Relative numbers | 0.71 | 0.66 | 0.64 |
| Addition numbers | 0.64 | $0.69^{H,O}$ | 0.61 |
| Causality | $0.65^{O}$ | $0.66^{O}$ | 0.55 |
| Noise | $0.85^{C,O}$ | 0.61 | 0.56 |
| Shape | $0.83^{C,O}$ | 0.68 | 0.64 |
| Tool use | 0.23 | $0.74^{H,O}$ | 0.38 |
| Tool properties | $0.71^{C,O}$ | 0.61 | 0.63 |
| Social | $0.74^{C,O}$ | 0.36 | 0.33 |
| Social learning | $0.86^{C,O}$ | 0.10 | 0.07 |
| Communication | $0.72^{C,O}$ | 0.57 | 0.55 |
| Comprehension | $0.84^{C,O}$ | 0.63 | 0.65 |
| Pointing cups | 0.72 | 0.74 | 0.73 |
| Attentional state | $0.59^{C,O}$ | 0.34 | 0.26 |
| Theory of mind | $0.65^{C,O}$ | 0.40 | 0.36 |
| Gaze following | $0.45^{C,O}$ | 0.22 | 0.17 |
| Intentions | $0.85^{C,O}$ | 0.59 | 0.56 |

Superscripts indicate that values are significantly higher than human (H), chimpanzee (C), or orangutan (O) values.

terested) performed better in the physical domain. In terms of inhibitory control, children showed a greater ability to inhibit than either ape species, and chimpanzees inhibited more readily than orangutans. There was a positive correlation for all three species of inhibitory control and cognitive performance in the physical, but not in the social, domain (*25*).

**Discussion.** The current results provide strong support for the cultural intelligence hypothesis that human beings have evolved some specialized social-cognitive skills (beyond those of primates in general) for living and exchanging knowledge in cultural groups: communicating with others, learning from others, and "reading the mind" of others in especially complex ways. Young human children who had been walking and talking for about 1 year, but who were still several years away from literacy and formal schooling, performed at basically an equivalent level to chimpanzees on tasks of physical cognition but far outstripped both chimpanzees and orangutans on tasks of social cognition. This was true at both the most general and the most specific levels of analysis, for individuals never before exposed to these tests, and across the most comprehensive test battery ever given to multiple primate species.

The current results provide no support for the general intelligence hypothesis that human cognition differs from that of apes only in general cognitive processes such as memory, learning, or perceptual processing, which should have led to children differing from apes in both the physical and social domains to an equal degree. However, we should note that because the children were somewhat more skillful than the apes in the causality tasks not involving active tool manipulation, as well as in the tasks of social cognition, it is possible that what is distinctively human is not social-cultural cognition as a specialized domain, as we have hypothesized. Rather, what may be distinctive is the ability to understand unobserved causal forces in general, including (as a special case) the mental states of others as causes of behavior (*22*, *23*, *26*). Even in this case, however, it is a plausible hypothesis that understanding hidden causal forces evolved first to enable humans to understand the mental states of other persons, and this generalized only later to the physical domain (*22*).

We may thus think of 2-year-old children's cognitive development in the physical domain as still basically equivalent to that of the common ancestor of humans and chimpanzees some 6 million years ago (with perhaps a little more sophisticated understanding of causality outside the context of tool use) but their social cognition as already well down the species-specific path. As one example, the finding that 2.5-year-old children's quantitative skills are basically equivalent to those of apes suggests a great ape "starting point" for human mathematical skills before serious instruction from adults (using written numerals) has begun (*27*). Also, another recent study found that young human children have preferences for spatial orientation similar to those of great apes, but older children have preferences that align with those of their culture, presumably as a result of experiencing their culture's ways of dealing with space, including the use of particular kinds of spatial language (*28*). This provides one example of the kind of cognitive transformation that may result from children using their specialized social-cognitive skills to participate in the cultural practices around them.

In terms of human evolution, it is likely that the crucial developments in skills of social-cultural cognition probably had not yet occurred in *H. erectus* 1 to 2 million years ago, because (i) their rapid pattern of brain growth during ontogeny was more similar to that of chimpanzees than to that of modern humans (*29*) and (ii) there are few signs in this early hominid of elaborate cultural differences between groups (*30*). The ecological conditions within which post–*erectus* humans' special skills of social-cultural cognition evolved are not known, but one hypothesis is that those skills evolved in support of especially complex forms of collaborative activity, such as hunting or gathering, supported by special skills of communication and social learning (*31*). These skills presumably grew out of earlier evolved primate skills of social cognition and learning in general, such as those that nonhuman primates display in their everyday interactions with groupmates in the wild, involving an understanding of the intentions, perceptions, and motivations of others (*24*).

It is certainly an issue that the test battery was both constructed and administered by humans. But in previous studies with these same tasks from the social domain, there is no evidence that the use of human versus conspecific interactants had any significant effect on performance (table S2) (*25*). And our temperament measures did not correlate with performance on the social domain of the test battery, which is where there were the largest differences among species (and indeed the children were more shy or less interested in general in the temperament task), providing no support for the notion that the apes related less well to the testing situation. In terms of test construction, we of course could have obtained different results with a different test battery. But the PCTB was constructed from a comprehensive theory of primate cognition based on the ecological tasks that primates face most commonly in both their physical and social environments. In general, we suspect that there would be more consensus among experts about the appropriateness of our tasks of physical cognition, whereas there might be more controversy about the social tasks. But a major factor in the choice of the social tasks was our focus on humans and the cultural intelligence hypothesis, and this meant testing those social-cognitive skills relevant to participation in culture by young children and then seeing the degree to which closely related species have these skills as well. It is perhaps relevant, in this regard, that domestic dogs (*Canis familiaris*) (which, in some sense, have been selected to live in human cultures) do not perform as well as chimpanzees on tasks of physical cognition but outperform them on tasks of social cognition (*32*, *33*).

The role played by individual variability and gender in our results requires further investigation. The finding that, at a very general level of analysis, there were no species differences in cognitive variability is somewhat unexpected, given that apes are much more genetically variable in general than are humans (*34*). Gender did not play a large role either. The one finding for gender with the apes (that male chimpanzees were better than female chimpanzees at space) fits with previous research. But our finding that human females were better than human males at tasks of physical cognition in general (and quantities in particular) does not fit so well with previous research (*35*), though not so much research has been done with children this young, and so there may be developmental differences involved.

The past few years have seen the sequencing of both the human and the chimpanzee genome (*36*–*38*) [the orangutan and bonobo (*P. paniscus*) genomes are currently being sequenced], with a major goal being to identify domains of human genetic distinctiveness. But to do this with specific reference to behavior and cognition, what is needed first are comprehensive and detailed comparisons among humans and closely related primates at the level of the phenotype, in terms of the actual behavioral and cognitive skills that have promoted survival and reproduction (*39*). A major avenue of future research is thus to use the PCTB to characterize the behavioral-cognitive phenotype of a wide variety of primate species. This could be done through systematic testing of carefully chosen representatives of the more than 50 genera of primates, which should then enable us to map out cladistically the evolution of primates' most important cognitive skills at the level of both the phenotype and, ultimately, the genotype.

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## Supporting Online Material

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# REPORTS

# Muscular Thin Films for Building Actuators and Powering Devices

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We demonstrate the assembly of biohybrid materials from engineered tissues and synthetic polymer thin films. The constructs were built by culturing neonatal rat ventricular cardiomyocytes on polydimethylsiloxane thin films micropatterned with extracellular matrix proteins to promote spatially ordered, two-dimensional myogenesis. The constructs, termed muscular thin films, adopted functional, three-dimensional conformations when released from a thermally sensitive polymer substrate and were designed to perform biomimetic tasks by varying tissue architecture, thin-film shape, and electrical-pacing protocol. These centimeter-scale constructs perform functions as diverse as gripping, pumping, walking, and swimming with fine spatial and temporal control and generating specific forces as high as 4 millinewtons per square millimeter.

Muscle cells are microscale linear actuators driven by the activation of actin-myosin motors, coordinated in space and time through excitation-contraction (EC) coupling (*1*, *2*). Structure-function relations are conserved over several orders of spatial magnitude, from the sarcomere to the muscle bundle, by virtue of a hierarchical architecture. These architectures are achieved by morphogenesis programs that are responsible for coupling a broad range of processes, from sarcomeregenesis to the integration of the biochemical and electrical networks that support muscle function (*1*). Muscle actuation occurs over a wide range of frequencies (0 to ~100 Hz), spatial dimensions (5 μm to ≥1 m), and force regimes (~5 μN to ≥1 kN) (*3*, *4*). Artificial muscles can match certain temporal, spatial, or force regimes typical of biological muscle (*5*, *6*), but they cannot fully replicate all of these capabilities, nor can they use the same high-density energy sources. Thus, engineered muscle remains an attractive method for building actuators and powering devices from the micro to macro scales.

Device design with engineered tissues faces many of the same technical challenges as therapeutic cardiac tissue engineering [reviewed in (*7*)], the most difficult of which is proper replication of morphogenetic coupling schemes in three dimensions. Tissue-engineered myocardium based on cardiomyocytes seeded into gels (*8*), rolled up from sheets (*9*), or released from surfaces (*10*) has demonstrated the potential to produce actuators (*11*), tissue grafts (*12*), and power microdevices (*13*). The utility of these techniques is limited by the geometry of the device, but recent work in soft lithography (*14*–*16*) has provided new techniques to replicate cell and tissue microenvironments in vitro, suggesting an alternative means of achieving the functionality of a three-dimensional (3D) device with a 2D tissue.

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We reasoned that to mimic the functionality of muscle bundles, a 2D engineered muscle tissue on a free-standing, flexible thin film would allow three degrees of freedom during contraction. We built 2D anisotropic cardiac tissues by culturing neonatal rat ventricular cardiomyocytes on polydimethylsiloxane (PDMS) elastomer thin films, muscular thin films (MTFs), which remained planar during myogenesis and then were shaped and released into 3D. Shortening of cardiomyocytes during synchronous contraction caused the PDMS thin film to bend during systole (contraction) and return to its original shape during diastole (relaxation). Based on the ability of these 2D planar shapes to adopt complex 3D conformations (*17*, *18*), we leveraged the inherent contractility of the cardiomyocytes to create a variety of proof-of-concept 3D actuators and soft robotic devices.

We engineered three kinds of 2D myocardial tissue: isotropic (Fig. 1, A to C), anisotropic 2D (Fig. 1, D to F), or an array of discrete muscle fibers (Fig. 1, G to I) by passive seeding of dissociated ventricular cardiomyocytes on fibronectin (FN)–coated or microcontact-printed (μCP) surfaces (*14*, *15*). Each tissue type was characterized by distinct differences in sarcomere alignment (i.e., direction of contractility) as well as electromechanical coupling (fig. S1) (*19*). Isotropic 2D myocardium had no net alignment of cell bodies (Fig. 1A) or sarcomeres (Fig. 1C). Anisotropic 2D myocardium had uniaxial alignment of cell bodies (Fig. 1D) and sarcomeres (Fig. 1F), fabricated by μCP of alternating high- and low-density FN lines based on previously described methods (*16*). The array of discrete muscle fibers was similarly fabricated by using μCP of FN lines and had uniaxial alignment of cell bodies (Fig. 1G) and sarcomeres (Fig. 1I). However, the electrical isolation between the fibers prevented spontaneous contraction of a single fiber from causing the entire MTF to contract (fig. S1). For both kinds of anisotropic tissue, the FN lines served as geometric cues for the inter- and intracellular organization of cardiomyocytes into a tissue and the uniaxial coupling of sarcomere ensembles over length scales from microns to centimeters.

Polymeric thin films were built by spin coating a thermally sensitive sacrificial layer of poly (N-Isopropylacrylamide) (PIPAAm) on glass cover slips and then spin coating a PDMS thin film on top of the PIPAAm (fig. S2) (*19*). The thickness of the PDMS film (14 to 60 μm) was controlled by varying the viscosity of the PDMS prepolymer and the spin-coating speed (fig. S3).

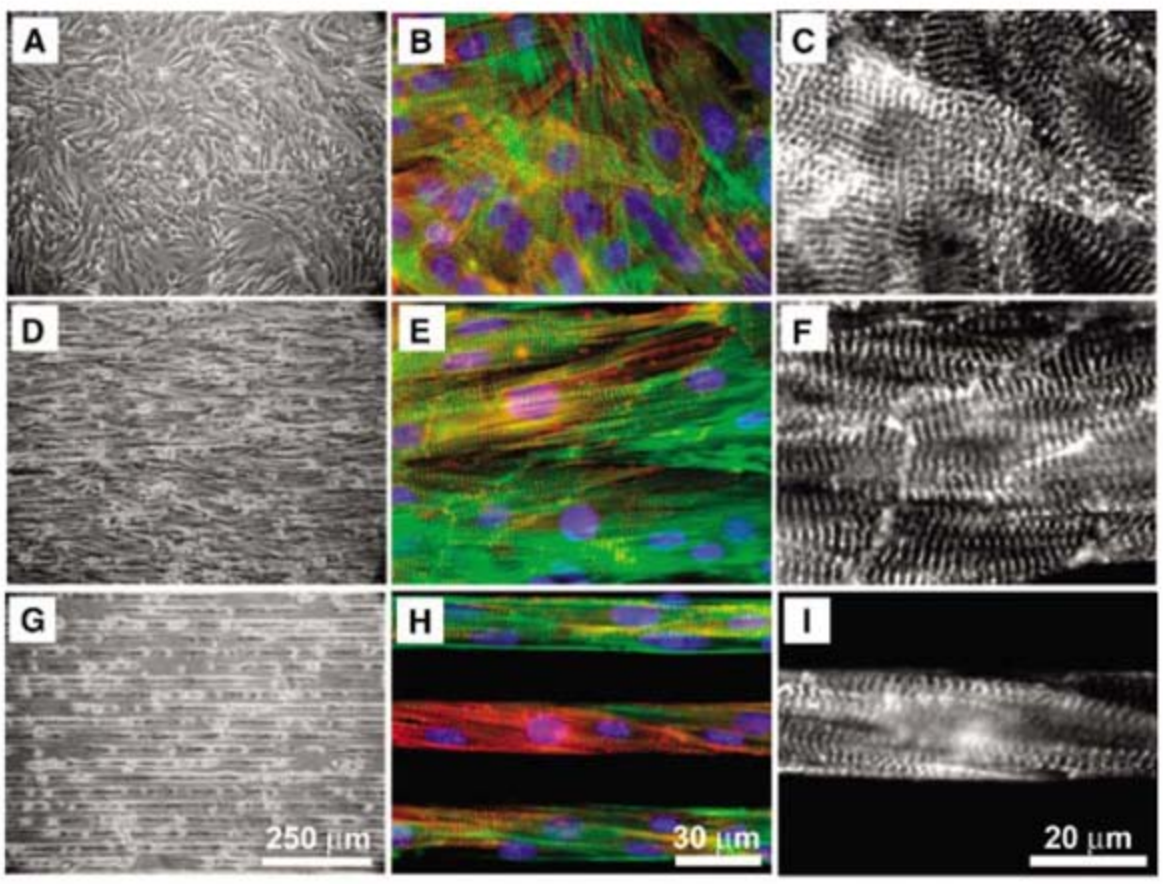


**Fig. 1.** The microstructure of the 2D myocardium was engineered to be isotropic or anisotropic to control contractility. Uniform FN coatings produced isotropic 2D myocardium (**A** to **C**) with no long-range order. (C) Staining for sarcomeric α-actinin revealed no preferential alignment of sarcomeres along any axis. Micropatterns of alternating high- and low-density 20-μm-wide FN lines (**D** to **F**) produced continuous anisotropic 2D myocardium. (F) Staining for sarcomeric α-actinin revealed uniaxial sarcomere alignment. Micropatterns of alternating 20-μm-wide lines of high density FN and Pluronic F127 (BASF Corp., Florham Park, New Jersey, USA) (**G** to **I**) produced an array of discrete muscle fibers. (I) Staining for sarcomeric α-actinin revealed uniaxial sarcomere alignment. Images are phase contrast [(A), (D), and (G)]; immunofluorescence of nuclei (blue), F-actin (green) and sarcomeric α-actinin (red) [(B), (E), and (H)]; and the signal from sarcomeric α-actinin alone [(C), (F), and (I)] to indicate and emphasize the direction of sarcomere alignment.

Once cured, cardiomyocytes were seeded onto the FN functionalized PDMS/PIPAAm–coated cover slips and cultured at 37°C for 4 to 6 days until a 2D myocardium was formed. At 37°C, PIPAAm was hydrophobic and remained solid when in contact with water, which ensured that the PDMS remained on the cover slip. When removed from the incubator and cooled to room temperature (~22°C), the desired MTF shape was manually prepared with a scalpel; aqueous dissolution of the thermally sensitive PIPAAm layer released the MTF. The PDMS thus served as a detachable, biocompatible substrate for the 2D tissue. Once in solution, the MTF spontaneously adopted a 3D conformation determined by its film properties or was fashioned to create more complex 3D shapes. While the cardiomyocytes provided either spontaneous or paced contractile function, the PDMS thin film allowed mesoscale sculpting of functional forms, restorative elasticity, and improved handling characteristics. Specifically, the PDMS film thickness dictated MTF bending stiffness, and its structural integrity allowed the muscle sheet to be formed into a variety of 3D shapes without disrupting the 2D muscle tissue.

The 3D deflection of MTFs depended on the direction of tissue alignment relative to the PDMS thin-film geometry (fig. S4 and movie S1). For example, on similarly sized rectangles, aligning anisotropic 2D myocardium along the width (fig. S4A), length (fig. S4B), and diagonal (fig. S4C) resulted in deformation along those axes with minimal deformation along the orthogonal axes. These results illustrate the relation between uniaxial sarcomere alignment (Fig. 1F) and contraction (fig. S4). A similar correlation has been reported between cardiomyocyte alignment and longitudinal and transverse conduction velocities in anisotropic 2D myocardium (*16*).

To test our hypothesis that the constructs would display biomimetic functionality, we fabricated simple oscillators, soft robotic actuators, and motile devices that could walk and swim. Soft robotic actuators were constructed with MTFs by controlling process parameters and EC coupling to dictate the 3D conformation of the free-standing construct and the contraction kinetics (*19*). Thin-film thickness (fig. S3) could be varied to control diastolic MTF conformation. The elastic modulus for Sylgard 184 PDMS elastomer is 1.5 MPa (*20*), whereas the elastic modulus for rat cardiomyocytes is ~30 kPa (*21*), a difference of two orders of magnitude. The MTF bending stiffness was dominated by the PDMS, which ranged from 0.5 to 30 μN/m. MTFs, for which the PDMS thickness was greater than ~25 μm, remained planar during diastole. In contrast, thinner films adopted a curved conformation as soon as the MTFs were released from the cover slips (Fig. 2), which defined two possible modes of systolic film bending, flexion, or extension. Which surface cardiomyocytes were on, convex or concave, was controlled by the cure temperature of the

PDMS, 22°C (room-temperature cure) or 65°C (heat cure), respectively (*19*). We designed a number of 2D shapes as templates engineered to adopt defined 3D conformations after release from the cover slip.

When MTFs with 2D myocardium on the concave surface contracted, the radius of film curvature decreased, bending the film further out of plane (flexion). For example, long rectangular strips with anisotropic 2D tissue aligned along their length (Fig. 2A). In this configuration, the MTF transitioned from a loosely rolled state (diastole) to a tightly rolled state (systole) during spontaneous, cyclic contractions (movie S2). The stress produced by this rolled MTF at peak systole was at least 15 kPa per contraction [calculated by measuring MTF radius of curvature at peak systole and solving a modified Stoney's equation (fig. S5) (*19*). MTF contraction was faster than relaxation; this temporal asymmetry was measured by plotting change in the diameter as a function of time (Fig. 2B and movie S2). This feature has application in valveless pumping of viscous fluids similar to the embryonic vertebrate heart tube by peristaltic action (*22*) or hydroelastic impedance (*23*). Further, these rolled MTFs are reminiscent of the laminar structure of the ventricle, where anisotropic sheets of cardiac muscle are wrapped to form a cavity whose blood-filled volume is reduced during systole (*24*).

When MTFs engineered with 2D myocardium on the convex surface contracted, the radius of film curvature increased (or even inverted), bending the film back in plane (extension). We made helical MTF actuators capable of cyclic, axial extension and rotation created by aligning an array of discrete muscle fibers 5° to 15° off-axis to the length of long PDMS rectangles (Fig. 2C). These constructs spontaneously adopted this helical conformation (like a paper towel tube), where the pitch was a function of the angle between the longitudinal axis of the anisotropic tissue and the midline of the thin film. Contraction of the MTF resulted in a decrease in helical pitch while maintaining a constant inner radius (movie S3), producing ~300 μm of axial extension and ~50° of circumferential rotation (Fig. 2D). Although this is in contrast to the rolling laminar structure depicted in Fig. 2A, this functional scheme is consistent with alternative theories of diastolic ventricular function which suggest that the ventricles can act as a suction pump (*25*).

We built a soft robotic gripper that uses electrical stimulation protocols to produce tonic contraction of the MTF with prescribed strength and grip radius (Fig. 2E and movie S4). An electric field was created using parallel, platinum wire electrodes on either side of the gripper, and a function generator controlled voltage amplitude (10 V, 10 ms pulse-width) and stimulation frequency (*19*). Specifically, pacing frequency was modulated from 0.25 to 5.0 Hz to control systolic bending of the gripper and hold the longitudinal ends at a prescribed separation (Fig. 2F). During contraction, the ends of the gripper come together until they touch and stop due to the contact force. Rather than simply opening and closing once, the gripper was switched from an open state (diastole) to a tonic, closed state during systole by increasing the pacing rate until the MTF entered tetanus at 5 Hz [generating constant stress in excess of 25 kPa (fig. S6)]. So, whereas gripping objects by hand is achieved by increased firing rate and motor unit recruitment, in our devices, we could accomplish this only with the former (*26*). Shaping and functionalizing of the distal ends of the gripper has potential for enabling tasks such as binding and manipulation of single cells and small biological samples.

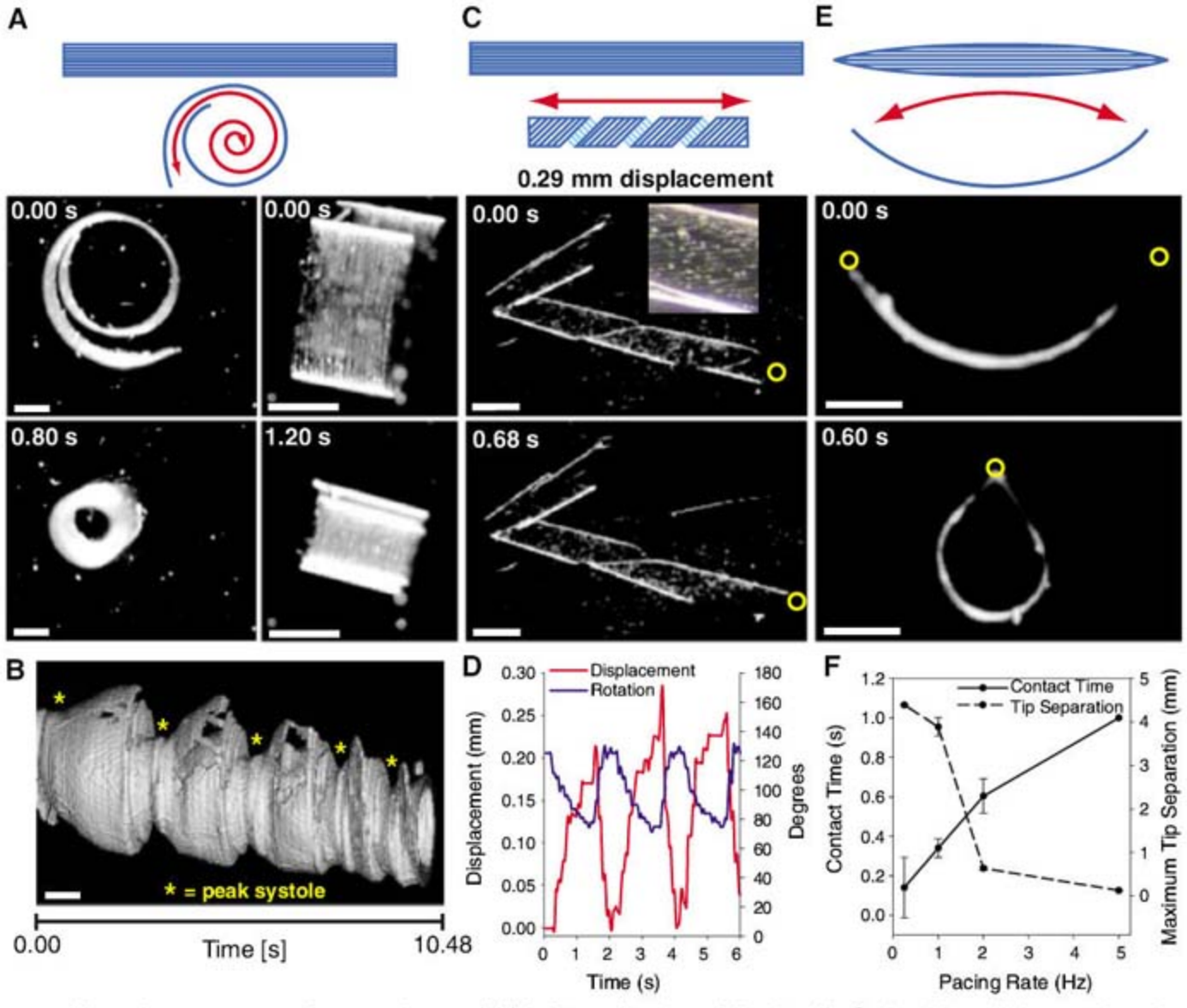


**Fig. 2.** MTFs were used to build soft robotic actuators with customized functionality. (**A**) The coiled strip had anisotropic myocardium (on the concave surface) aligned along the rectangle length that cyclically contracts from an uncoiled to coiled state. (**B**) This is a 3D plot of the coiled strip's diameter as a function of time, where peak systole is noted with asterisks. This shows the temporal asymmetry between the rapid coiling rate (contraction) compared with the slower uncoiling rate (relaxation). (**C**) The helical linear actuator was a rectangular strip with discrete arrayed muscle fibers [on the convex surface (see inset)] that spontaneously adopted a helical conformation. (**D**) Tracking the tips [yellow circles in (C)] shows cyclic extension and rotation at 0.5 Hz pacing. (**E**) The "gripper" was a long, rectangular strip with lengthwise-aligned anisotropic myocardium (on the concave surface) that brought the tips together upon contraction. (**F**) Tracking the tips [yellow circles in (E)] as a function of pacing rate demonstrated control of diastolic tip separation and the period the gripper was closed per second (error bars represent SD). For each MTF, the schematic illustrates the 2D shape and cardiomyocyte alignment before release and the subsequent 3D conformation [red arrows in (A), (C), and (E) indicate direction of film bending]. The video still images show the construct in diastole at time 0.00 s and in systole 0.60 to 1.20 s later. Scale bars, 1 mm.

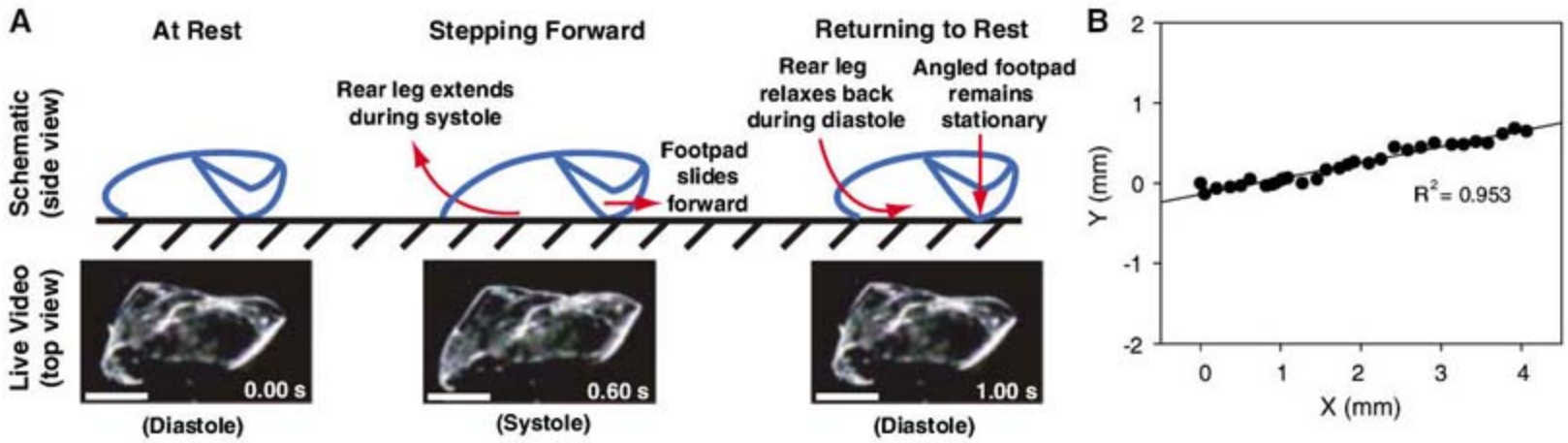


**Fig. 3.** Myopod capable of autonomous or remote-controlled walking. The myopod was formed from a triangle MTF, with isotropic myocardium (on the convex surface) manually folded into a 3D shape. (**A**) The motion is illustrated in a schematic side view and live top view as it starts in diastole and steps forward during systole. During systole the myocardium contracted, causing the "leg" to extend and push the myopod forward. As the leg relaxed during diastole, the angled footpad prevented the myopod from slipping backward. (**B**) Frame-by-frame video tracking of the front of the myopod at 1-s intervals (denoted by black dots; linear regression denoted by solid line) shows consistent and directed locomotion at a speed of ~8 mm/min at 1 Hz pacing (10 V amplitude). Myopod relative velocity (~2.7 lengths/min) is similar to that reported by Xi *et al.* (~3.7 lengths/min) for their muscle-powered microdevice (*13*); however, the myopod can be reconfigured by refolding it into another conformation and does not require microfabrication to build. Scale bars, 1 mm.

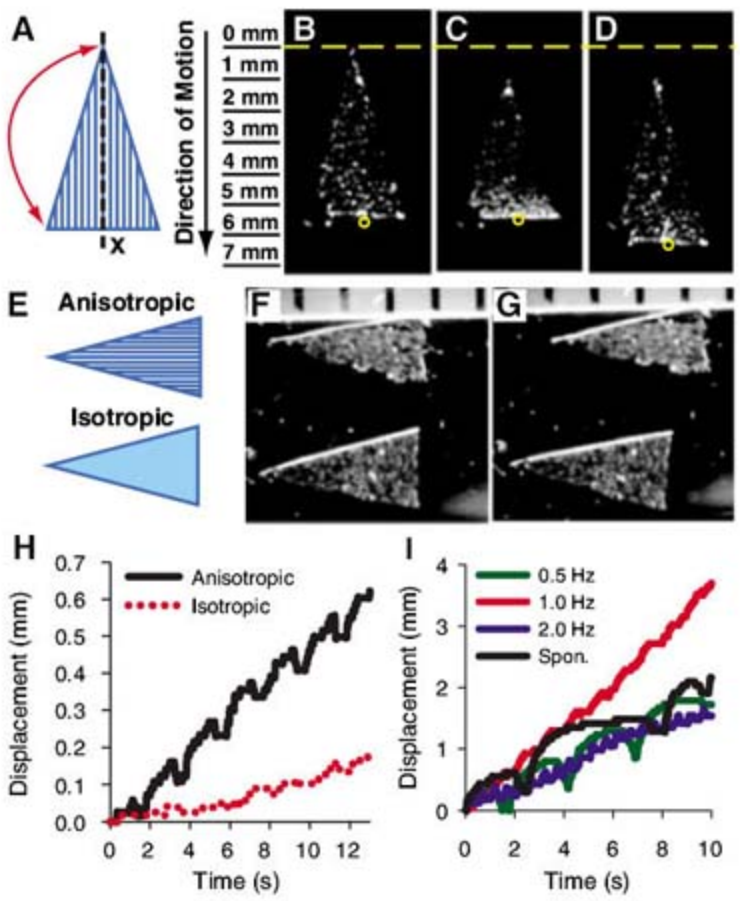


**Fig. 4.** The triangular MTF swimmers demonstrate that tissue microstructure, film shape, and pacing rate collectively contributed to motility. (**A**) The MTF triangle swimmer was realized by aligning anisotropic myocardium parallel to the height of the triangle (red arrows denote direction of film bending). Tracking the MTF through subsequent video frames showed that (**B**) the relaxed construct contracts by (**C**) pulling the tail (tip) of the triangle in toward the base. (**D**) As the triangle relaxed and returned to its original shape, it produced a propulsive force that drove the MTF forward. (**E**) Comparison of similarly shaped triangle swimmers with anisotropic or isotropic myocardium revealed the importance of tissue structure in potentiating motility. At 0.5 Hz pacing, the anisotropic swimmer, (**F**) starting from rest, (**G**) surged ahead after 13 s. (**H**) Tracking frame-by-frame displacement showed that the anisotropic swimmer was ~5 times as fast as the isotropic swimmer. (**I**) The anisotropic swimmer's velocity was a function of pacing rate, revealing a maximum swimming rate of ~24 mm/min at 1.0 Hz pacing. Pacing voltage was 10 V except for spontaneous contractions in (I). Ruler markings in (F) and (G) are 1 mm.

We can engineer MTF actuators with many functional shapes, but do they generate enough force to be useful? Isometric contraction of MTFs demonstrated specific forces of 1 to 4 mN/mm$^2$ (fig. S7), comparable to tissue engineered myocardium (*8*, *9*) and native cardiac muscle (*19*). Unlike artificial muscles, MTFs demonstrate moderate contractile forces, high strain, fast actuation, and low power consumption (*5*, *19*). On the basis of these findings, we reasoned that MTFs could move by mimicking the locomotion of simple organisms.

MTFs were engineered for use as autonomous, or remotely controlled, soft robotic vehicles. In this context, remote control refers to control of contraction rate using electrical field stimulation. Locomoting constructs, myopods, were designed to walk along the bottom of a Petri dish in a directed path under spontaneous or paced contractions (Fig. 3 and movie S5). The myopod was formed from a triangular MTF with isotropic 2D myocardium (Fig. 1A) rather than the anisotropic 2D myocardium (Fig. 1D), demonstrating that, in this case, microscale control of tissue microstructure was not required for motility. Rather, the spatial symmetry break was achieved by folding the tip of the triangle into a loop reattached midway along the height to create a footpad (Fig. 3A). The MTFs reconfigure because the exposed PDMS is hydrophobic on the non-cell side, which sticks to itself in aqueous solution and provides a convenient way to fabricate complex 3D shapes. When paced, the myopod moved with constant velocity (Fig. 3B).

We reasoned that 2D MTFs could replicate the anguilliform swimming motion of a *Basilosaurus* with properly engineered tissue registered to the appropriate thin-film geometry. Autonomous and remotely controlled swimming MTFs were engineered from ~30-μm-thick PDMS films cut into isosceles triangles with the anisotropic myocardium assembled parallel to the height of the thin film (Fig. 4A). Field stimulation induced a propagating contractile wave (Fig. 4, B to D) that resulted in increasingly greater orthogonal deflection of the MTF toward the tip. Comparing similar triangle swimmers with isotropic or anisotropic 2D myocardium (Fig. 4E and movie S6) demonstrated that tissue microarchitecture was critical in potentiating mobility. During a typical experiment (Fig. 4, F and G), the anisotropic swimmer traveled ~5 times as far, with an average velocity of 3 mm/min. The isotropic tissue failed to contract in a manner necessary for generating propulsion, twitching and drifting at a rate of 0.6 mm/min (Fig. 4H).

As in the case of the soft robotic gripper, the electrical pacing protocol applied to the MTF swimmer could be tailored to maximize swimming velocity and minimize the metabolic cost (i.e., maximize distance traveled per contractile cycle) (Fig. 4I and movie S7). The swimming motion was separated into two phases, burst (systole) and coast (diastole, passive propulsion). This swimming technique is used by species such as the zebrafish, where a single tail flip is followed by a phase where the fish keeps its body straight (*27*). Maximum velocity (24 mm/min)

was achieved at 1 Hz pacing frequency by taking advantage of this velocity profile (Fig. 4I). Slower pacing at 0.5 Hz resulted in periodic dips in the velocity as the coasting speed deteriorated before the next contractile cycle. Faster pacing at 2 Hz interrupted the power stroke before it was completed. These findings show that the stimulation frequency may be varied to optimize MTF function. Zebrafish larvae transition from low to high Reynolds number swimming by increasing tail-beat frequency and bend amplitude (degrees) and shifting bend location, which suggests that similar performance is possible with MTF swimmers (*28*). We have scaled this swimming behavior from $Re$ ~0.1 to ~10 for 2 mm to 1.2 cm length-scale MTF swimmers. It should be possible to scale-up these swimmers further (to $Re > 100$), because zebrafish use the same burst-and-coast behavior from larvae (~4 mm) to adult (~35 mm) length-scales (*27*).

Can we leverage these capabilities to build more advanced soft robotic actuators and devices? One possibility is to borrow biological design principles from organisms such as octopi that use elastic, muscular appendages for complex movements such as bipedal locomotion and articulated joints (*29*). Another is to scale-up force generation by increasing the thickness of the 2D myocardium or by combining multiple MTFs in parallel. Beyond devices, analysis of MTF deformation during contraction also has potential for studying biomechanics of myocardial sheets as a model for the laminar muscle of the ventricular wall.

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### Supporting Online Material

www.sciencemag.org/cgi/content/full/317/5843/1366/DC1
Materials and Methods
SOM Text
Figs. S1 to S7
Movies S1 to S7

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# Imaging of Arsenic Cottrell Atmospheres Around Silicon Defects by Three-Dimensional Atom Probe Tomography

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Discrete control of individual dopant or impurity atoms is critical to the electrical characteristics and fabrication of silicon nanodevices. The unavoidable introduction of defects into silicon during the implantation process may prevent the uniform distribution of dopant atoms. Cottrell atmospheres are one such nonuniformity and occur when interstitial atoms interact with dislocations, pinning the dislocation and trapping the interstitial. Atom probe tomography has been used to quantify the location and elemental identity of the atoms proximate to defects in silicon. We found that Cottrell atmospheres of arsenic atoms form around defects after ion implantation and annealing. Furthermore, these atmospheres persist in surrounding dislocation loops even after considerable thermal treatment. If not properly accommodated, these atmospheres create dopant fluctuations that ultimately limit the scalability of silicon devices.

The controlled placement of dopant atoms and the subsequent creation of point defects in Si form the basic materials used to fabricate semiconductor field-effect devices. Each electrically "active" dopant atom contributes an electrical carrier to the lattice. A nonhomogeneous distribution of dopant atoms, as measured over the nanoscale regime, could create a corresponding fluctuation in the electrical characteristics of that region. In macro-sized devices, these localized fluctuations average out over the relatively large area of the device and therefore have a negligible impact on overall performance. Now that device scales are reaching the nanometer regime, localized fluctuations are having an increasingly important impact on the electrical characteristics of individual devices. Imaging of individual dopant atoms is essential to the development of advanced nanoscale devices and is therefore an area of intense interest among the semiconductor community (*1*–*4*).

Si wafers are most often doped with As, P, or B atoms. Because of the relatively large size of the As atom, its diffusivity is orders of magnitude lower than that of P or B. This low diffusivity makes As a desirable candidate for nanometer-scale device technology (*5*, *6*). The ion implantation of dopant atoms, particularly the heavier As ions, almost always results in the simultaneous creation of undesired defects. The subsequent evolution of these defects as a function of thermal annealing is well documented (*7*–*9*). After ion implantation, the Si lattice is heavily damaged or possibly amorphized because the Si atoms have been ballistically removed from their lattice sites. The result is a high concentration of interstitial Si atoms, $Si_I$, with a corresponding supersaturation of Si vacancies, $V_{Si}$. The application of a small amount of thermal energy (~400° to 600°C) is sufficient to repair the Si crystal structure. In reasonably pure Si, the $Si_I$ atoms coalesce into energetically favorable {311} rod-like defects (*8*, *9*). Where a high areal concentration ($> \sim 10^{14}/cm^2$) of impurity atoms is present, the $Si_I$ atoms instead form into spheroidal defects of varying size (*8*, *10*). During continued thermal treatment, the spheroidal defects coalesce and grow into larger de-

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fects, following an Ostwald-ripening process. Continued thermal treatments result in the complete dissolution of the original defects in favor of dislocation loops aligned along the {111} plane (*9*, *11*). These loops are stable against continued thermal annealing even to temperatures that exceed 1000°C.

When interstitial impurity atoms interact with a dislocation, Cottrell atmospheres may form (*12*). Interstitial atoms—for example, As atoms in Si—distort the lattice slightly, causing a strain field around the interstitial. When the interstitial atom diffuses into the proximity of a dislocation, the strain field relaxes when the interstitial moves into the dislocation. Because this is an energetically favorable state, both the dislocation and the interstitial are pinned. The presence of Cottrell atmospheres in implanted Si may help to explain and to predict the evolution of dislocation loops in Si.

Secondary ion mass spectrometry (SIMS) and transmission electron microscopy (TEM) have been used to correlate indirectly the presence of dopant atoms with the evolution of defects, and detailed models have been proposed to account for these experimental correlations (*7*–*11*). However, unambiguous quantitative information regarding the precise location of individual dopant atoms relative to the known defects has not been available.

Laser-assisted atom probe tomography (APT), a technique capable of rapidly analyzing large volumes of non–electrically conducting material, can provide three-dimensional (3D) mapping of individual dopant and other impurity atoms within Si (*13*–*25*). The technique involves application of a high voltage to the base of a cryogenically cooled, needle-shaped specimen and continuous pulsing of the tip of the specimen with a focused laser. In the case of Si, the sample is formed into a needle-shaped specimen with a focused ion beam (*26*, *27*). The applied voltage creates a high electric field, 20 to 40 V/nm, at the apex of the needle. The laser pulse temporarily heats the specimen tip,

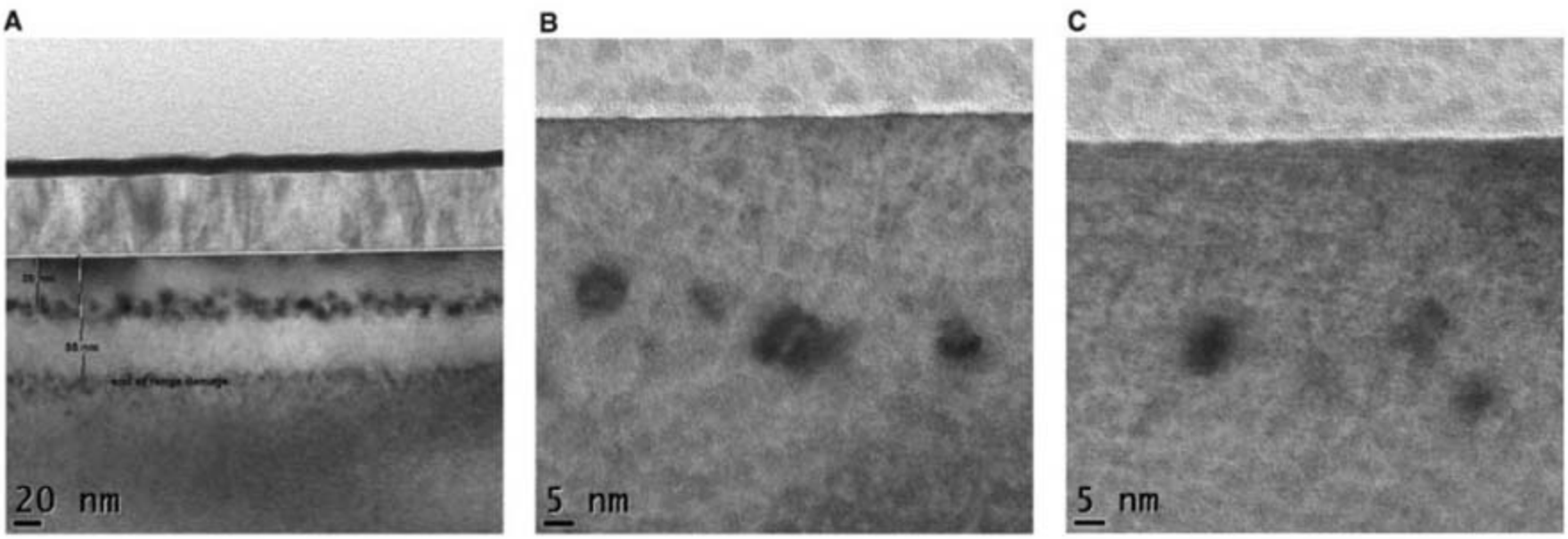


**Fig. 1.** (**A** to **C**) TEM images showing the As-rich defect region and the end-of-range damage layer after annealing at 600°C for 30 min.

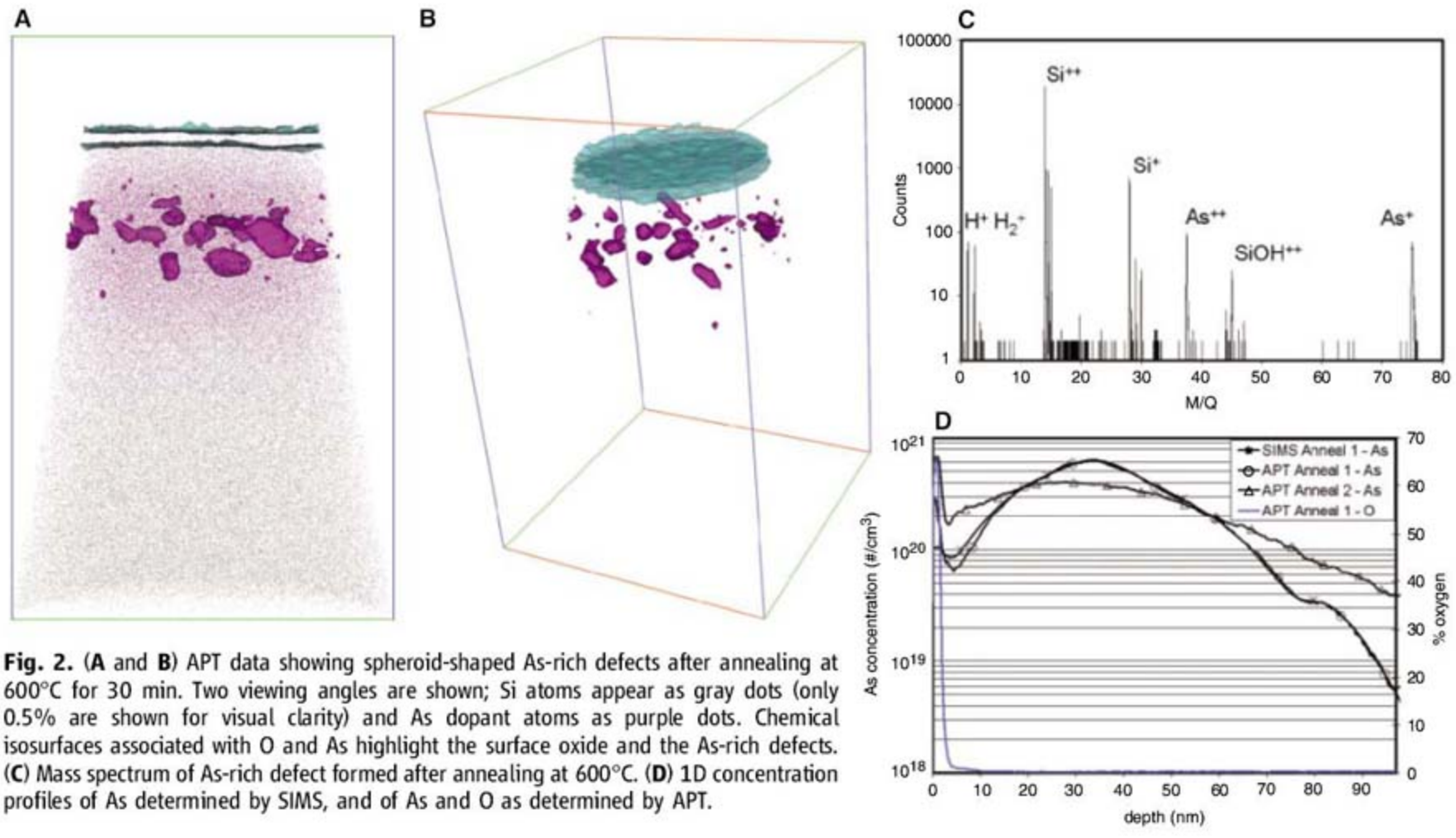


**Fig. 2.** (**A** and **B**) APT data showing spheroid-shaped As-rich defects after annealing at 600°C for 30 min. Two viewing angles are shown; Si atoms appear as gray dots (only 0.5% are shown for visual clarity) and As dopant atoms as purple dots. Chemical isosurfaces associated with O and As highlight the surface oxide and the As-rich defects. (**C**) Mass spectrum of As-rich defect formed after annealing at 600°C. (**D**) 1D concentration profiles of As determined by SIMS, and of As and O as determined by APT.

providing just enough thermal energy for a single ion to escape from the end of the needle. The liberated ion follows the field lines to a collector plate, which provides the *X-Y* spatial resolution. The sequence of evaporation events provides the depth, or *Z*, dimension. The timing of the pulsed events enables mass resolution via time-of-flight spectroscopy. The result is the atom-by-atom mapping of a material of interest with a spatial resolution on the order of the atom locations, or ~0.2 to 0.4 nm. This resolution is sufficient to describe dopant atom positions relative to and within local defects (*19*–*25*).

The samples for analysis were created by implanting $2 \times 10^{15}$ As atoms/cm$^2$ at an accelerating energy of 50 keV into {100} Si. The wafers were tilted at 7° to the ⟨100⟩ plane during the implant. The first sample underwent annealing at 600°C for 30 min. The second sample underwent the same annealing at 600°C followed by additional annealing at 1000°C for 30 s.

Figure 1 shows TEM images for the sample that underwent the 600°C anneal. Two defect regions are apparent. The expected end-of-range damage region occurs 85 nm into the sample. At a depth of 35 nm, there exists a second damage region associated with a high concentration of As atoms. The high-resolution images show that these defects are spheroidal in nature and that some of the defects have already started to evolve into dislocation loops. In addition to the defects, the images show a native oxide layer, ~2 nm thick, on the surface of the sample.

The 3D atom map obtained via APT analysis is shown at two different viewing angles in Fig. 2, A and B. Knowledge of the atom identities and locations allows for the construction of isoconcentration surfaces around regions of unique chemical composition. In this case, an O isosurface is constructed at 10 atomic % O, which highlights the surface oxide. The chemical roughness of this layer is calculated at 0.3 nm. Isoconcentration surfaces may similarly be drawn with respect to the As atoms. In this case, such a surface was defined at an As concentration of 2 atomic %. The surfaces display spheroidal regions of Si, inside of which the As concentration exceeds 2 atomic %. Correlation of Figs. 1 and 2 indicates that these As regions occur at the same depth below the sample surface as the defects observed by TEM and are therefore assumed to be directly associated with the defects imaged by TEM.

Figure 2C displays the mass spectrum as obtained from several of the As-rich defects. In this spectrum, there are 52,887 ± 230 Si atoms and 2539 ± 48 As atoms in the displayed defects, indicating an As concentration of 4.8 atomic %. The background As concentration in the region of the defects is 1.2 atomic %, indicating that the actual As atoms trapped within the defect represent 3.6 atomic % of the atoms. The excess impurity concentration at a defect site, relative to the background impurity concentration, can be defined as $C_{As} = C_{As}^{\circ} \exp(u/kT)$, where $C_{As}$ is the localized As concentration, $C_{As}^{\circ}$ is the background As concentration, $k$ is Boltzmann's constant, $T$ is the formation temperature, and $u$ is the binding energy between the defect and the excess impurity atom. In the case of the 600°C anneal studied here, a binding energy of 0.1 eV is calculated for the As atoms trapped within the identified defects.

Atomic concentration as a function of depth into the wafer can be determined by both APT and SIMS. We used both methods to obtain these profiles for As, and APT to obtain them for O (Fig. 2D). Overall, the results correlate well. The 2-nm-thick native oxide is apparent in the atom probe measurement. Considerable As segregation into the oxide is revealed. The APT indicates As in the native oxide at a concentration of $3 \times 10^{20}$/cm$^3$, whereas SIMS analysis indicates $10^{20}$/cm$^3$. APT provides equal collection efficiencies for atoms across the mass spectrum, whereas SIMS analysis at interfaces suffers from aberrations associated with variable sputter and ionization rates as a function of material type (*28*–*31*). APT therefore provides a more accurate analysis than SIMS at the interface of dissimilar materials.

The As profile reaches a peak concentration of $6 \times 10^{20}$/cm$^3$ at a depth of 35 nm, which is the location of the As-rich defects. No anomalies in the 1D concentration profile are detected in this region. Both analyses, however, demonstrate a flattening of the As concentration profile in the 75- to 85-nm region, immediately before the end-of-range damage. It is interesting that the trapping of As atoms in the end-of-range damage layer is sufficient to distort the 1D concentration profile, whereas the As-rich defects, which trap far more As atoms than occur in the end-of-range region, do not distort the concentration profile.

Figure 3 shows TEM images of the sample after further annealing at 1000°C for 30 s. The

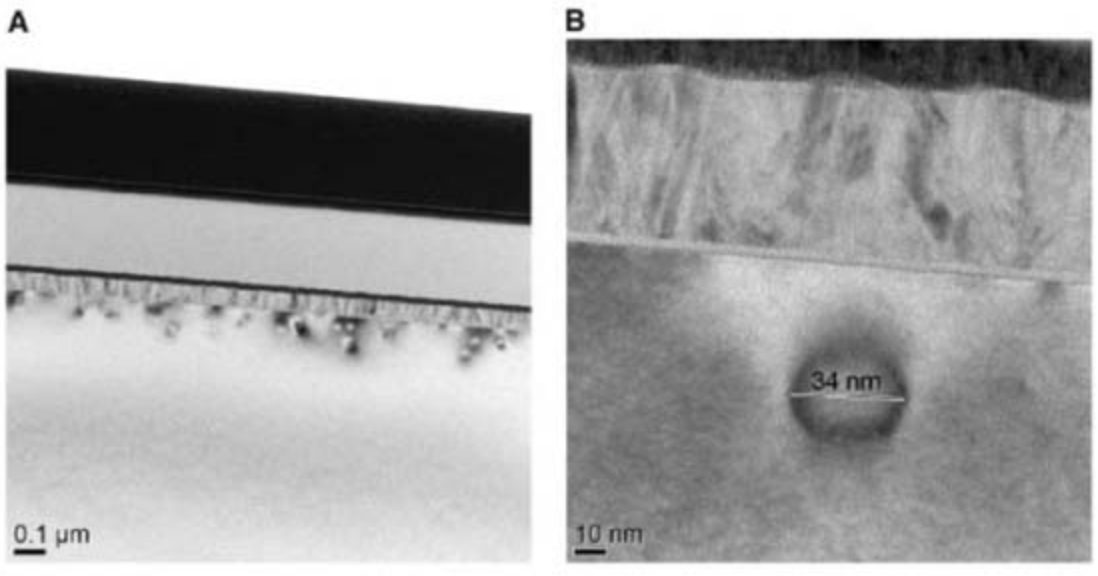


**Fig. 3.** (**A** and **B**) TEM images for the As-implant sample after annealing at 600°C for 30 min, then at 1000°C for 30 s. (**C**) EDS analysis of As in dislocation loop.

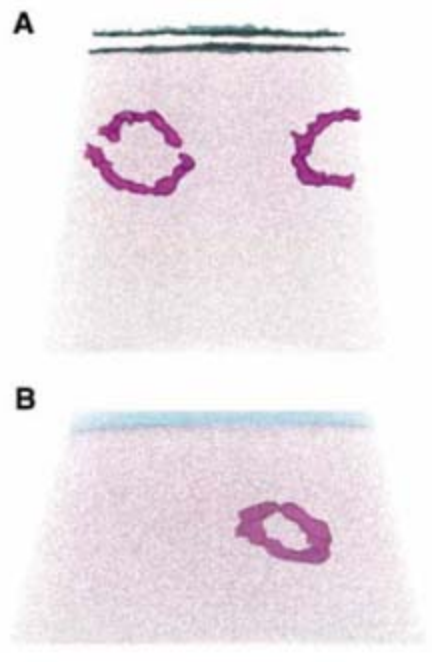


**Fig. 4.** (**A** and **B**) APT data on As-implant sample after annealing at 600°C for 30 min, then at 1000°C for 30 s, showing As atoms trapped in dislocation loops. Si atoms (only 0.5% are shown for visual clarity) appear as gray dots, oxygen atoms as light blue dots, and As dopant atoms as purple dots.

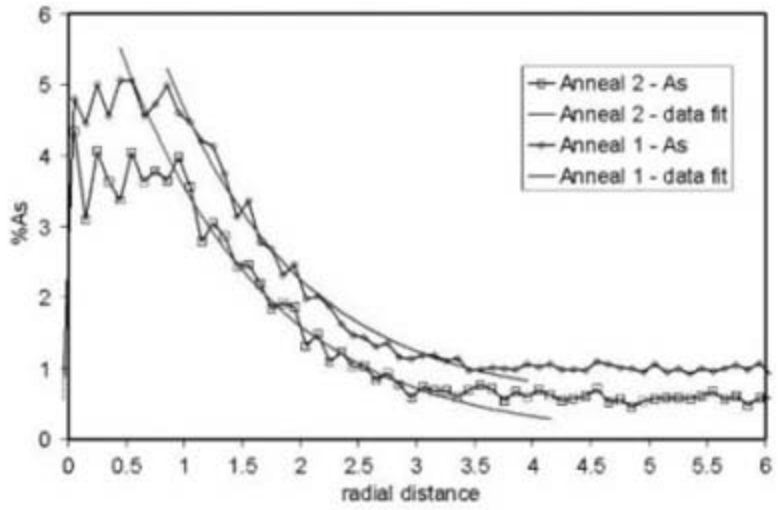


**Fig. 5.** Proximity histogram of As concentration in dislocation loop as measured from center to edge.

end-of-range defects have completely dissolved, and the spheroidal defects have transformed into dislocation loops. The loops remain in the As-rich region of the sample and are aligned along the {111} plane. An elemental map of a region containing a loop was obtained at 1-nm resolution by energy-dispersive spectroscopy (EDS) analysis. A concentration profile across the loop extracted from the As map (Fig. 3C) implies an As accumulation up to 3.3 atomic % around the edges of the dislocation loop, with a background As concentration of ~1.5 atomic %.

Figure 4 shows 3D atom maps of the As-implanted sample after annealing at 1000°C for 30 s; each map represents a separate analysis. The ~2-nm surface oxide is again apparent. The chemical roughness of this layer was calculated at 0.3 nm. The first analysis shows one full loop and one half loop; the second analysis shows one full loop. Isoconcentration surfaces were again drawn with respect to the As atoms at an As concentration of 2 atomic %. The surfaces display ring-shaped defects correlating to the dislocation loops seen in the TEM.

Chemical analysis of these dislocation loops shows that the two complete loops in Fig. 4 have 26,429 ± 162 and 37,665 ± 194 Si atoms, and 975 ± 31 and 1409 ± 37 As atoms, respectively. The half loop contains 15,672 ± 592 Si atoms and 592 ± 22 As atoms. The average As concentration in these loops represents 3.7 atomic % of the material composition compared to an As background of 0.8 atomic % ($4 \times 10^{20}/cm^3$) in this region. Hence, the As trapped in the loop comprises 2.9 atomic % of the total atoms within the loop. Again we measured the binding energy of the As atoms to the dislocation loops. After annealing at 1000°C, the binding energy had increased to 0.17 eV.

A direct comparison of the amount of As trapped in each defect type shows that during the transformation from spheroidal defects to dislocation loops, As atoms migrated from the spheroidal defects back into the bulk Si. Once freed from the defect, the As atoms could diffuse and possibly occupy a $V_{Si}$. This is consistent with the behavior of $Si_I$ atoms, which, although originally trapped in post-implant defects, are emitted back into the Si lattice upon thermal annealing.

The 1D As concentration profile, as obtained in the depth direction, is shown in Fig. 2D. The As segregation has increased to $9 \times 10^{20}/cm^3$, the profile shape has broadened, and the As profile has smoothed out in the end-of-range damage region now that the end-of-range defects have dissolved.

The As is distributed about the defect in a delocalized volume a few nanometers in extent. This distribution is indicative of a Cottrell atmosphere. Cottrell atmospheres, first described in 1947 (*12*) and later observed experimentally (*19*), appear as a cloud of impurity atoms surrounding dislocations. When the interstitial atoms migrate into the proximity of a dislocation, the strain field relaxes as the interstitial moves into the dislocation. This state is energetically favorable for both the dislocation and the interstitial atom. Proximity histograms of As atoms, as monitored radially away from the dislocation loop or spheroidal defect edges, are shown in Fig. 5. The data for each case are fit to an exponential function. For the spheroidal defects in the 600°C anneal case, the relation is $As(r) = 4.8 \exp(-0.86r)$, and for the dislocation loops in the 600°C plus 1000°C anneal case, the relation is $As(r) = 3.7 \exp(-0.8r)$, where $r$ is the radial distance from the edge of the As loop. It is interesting that the exponential decay in both cases is about the same. This similarity persists despite the difference in measured binding energy, 0.1 eV versus 0.17 eV. The decaying exponential relationship described here indicates that the trapping and subsequent release mechanism of the defects create concentration gradients localized on the nanometer scale.

The impact that these Cottrell atmospheres may have on the concentration of electrically active dopant atoms—and therefore on device performance—remains undetermined but could prove important. Consider the smallest device on a processor manufactured using 90-nm technology. This device has channel lengths on the order of 50 nm. The measured Cottrell atmospheres in Fig. 5 indicate a factor of 10 increase in As concentration over a ~3-nm region. It is therefore unlikely that the localized dopant concentration increase caused by the As Cottrell atmosphere would cause a noticeable electrical impact in a 90-nm device. Now consider the upcoming 22-nm technology node, with minimal features on the order of ~10 nm. The presence of a single-dopant Cottrell atmosphere within such a device could alter the electrical performance of the individual device in a way that renders it nonfunctional, or at least renders it dissimilar to an identical device that did not contain a Cottrell atmosphere.

The defects resulting from a high-dose ion implantation process and subsequent high-temperature anneal were analyzed and quantified with a combination of TEM, APT, and SIMS. Together these techniques showed that ion implantation initially causes the formation of spheroidal defects with trapped As atoms. The transformation of these defects into dislocation loops, as a function of high-temperature annealing, also results in the formation of As Cottrell atmospheres associated with these dislocations. These findings may have implications for dopant control in implanted Si as the scale of doped regions approaches the scale of the defects.

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# Soft X-ray–Driven Femtosecond Molecular Dynamics

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The direct observation of molecular dynamics initiated by x-rays has been hindered to date by the lack of bright femtosecond sources of short-wavelength light. We used soft x-ray beams generated by high-harmonic upconversion of a femtosecond laser to photoionize a nitrogen molecule, creating highly excited molecular cations. A strong infrared pulse was then used to probe the ultrafast electronic and nuclear dynamics as the molecule exploded. We found that substantial fragmentation occurs through an electron-shakeup process, in which a second electron is simultaneously excited during the soft x-ray photoionization process. During fragmentation, the molecular potential seen by the electron changes rapidly from nearly spherically symmetric to a two-center molecular potential. Our approach can capture in real time and with angstrom resolution the influence of ionizing radiation on a range of molecular systems, probing dynamics that are inaccessible with the use of other techniques.

Ultrashort light pulses in the infrared (IR), visible, and near ultraviolet (UV) regions of the spectrum are used extensively in many experiments to uncover the detailed dynamics of the transition states involved in chemical reactions (*1*–*5*). To date, studies of this type have been limited to relatively low-lying electronic states in atoms and molecules that can either be directly excited by absorbing a visible/UV photon or indirectly excited with multiphoton excitation techniques (*2*–*6*). However, common processes in nature, such as photoionization of atmospheric molecules induced by soft x-ray solar irradiation, create highly excited states by selectively ejecting an inner-shell electron or by simultaneously exciting more than one electron in a molecule. These states are simply not directly accessible using visible or UV ultrafast photons. Indirect excitation with multiphoton techniques also cannot populate these highly excited states, because this approach tends to strip electrons in a stepwise manner, starting with the least-bound electrons. Therefore, to capture dynamics initiated by an ionizing event in an atom or molecule, a fast (femtosecond) pump pulse with a photon energy in excess of tens of electron volts is required. Such photoionization dynamics play an important role in the atmospheric chemistry of the planetary systems (*7*, *8*). Moreover, the physics of photoionization underlies virtually all interactions of ionizing radiation with matter.

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This field of radiation chemistry, which seeks to understand how ionizing radiation interacts with chemical systems (*9*), has made considerable progress in the past decades through the use of synchrotron and plasma light sources. However, so far these studies have not achieved the femtosecond time resolution necessary to directly observe radiation-induced dynamics. Fourth-generation sources (e.g., ultrashort-pulse free-electron x-ray lasers) are currently being developed, in part to make such studies possible.

Laser-generated high-order harmonics can be used to produce bright, coherent beams of short-wavelength light with ultrashort pulse duration. In high-harmonic generation, an intense ($>10^{14}$ W cm$^{-2}$) femtosecond IR laser pulse is focused into a gas. The extreme nonlinear-optical interaction coherently upshifts the incident laser light into the soft x-ray and even the kiloelectron volt photon-energy range (*10*). Because photoabsorption cross sections for most molecules are largest for photon energies ranging from 12- to 120-eV (*11*), high harmonics are an ideal source for molecular excitation. Furthermore, their very short pulse duration and perfect synchronization with the driving laser pulse presents the intriguing possibility of studying electronic and nuclear dynamics with femtosecond and even attosecond resolution (*12*).

Up to this point, a few pioneering studies have used high-harmonic light to explore ultrafast dynamics in atoms (*13*), molecules (*14*, *15*), and solids (*16*). For example, in recent work a soft x-ray pulse was used to ionize and highly excite Xe, populating a number of shakeup states with low probability (*13*). The lifetimes of the resultant Auger decay were then confirmed to be 6 and 31 fs, in agreement with previous spectral measurements. In molecular systems, however, x-ray ionization can initiate complex dynamics that are much less well understood than in the atomic case, involving many excited and correlated electron channels that cannot be easily calculated and exhibiting complex spectra that cannot be understood on the basis of spectral measurements alone. Therefore, time-resolved measurements of x-ray driven dynamics in molecules can play a critical role in helping us to develop a better understanding of these concepts. However, ultrafast, femtosecond-duration x-rays have not previously been used as an ionizing pump beam to initiate dynamics in molecules. The available flux to date was simply too small to excite a sufficient fraction of molecules in any sample to use standard techniques, such as transient absorption spectroscopy, to observe x-ray–initiated dynamics.

Fortunately, other, more selective spectroscopic approaches can be successfully employed, as we demonstrated using coincident electron-ion three-dimensional momentum imaging. This technique efficiently collects ionized molecular fragments in coincidence, making it possible to fully reconstruct a single ionization and fragmentation event. This reaction microscope (*17*) technique has been used very successfully for a variety of studies of atomic and molecular processes, in both femtosecond-laser and synchrotron experiments (*18*, *19*).

We used this type of reaction microscope (Fig. 1) to observe the dissociation of a molecule ionized by soft x-ray radiation in real time. In our experiment, a few-femtosecond soft x-ray pulse ionizes $N_2$ by ejecting an electron from the valence or inner valence shells. The molecule is left in one of the many highly excited states of $N_2^+$, which then dissociate into an ion and a neutral atom. Using the reaction microscope, we can detect electrons and ions in coincidence, and from that information we can identify the different ionization and dissociation channels involved as the excited molecule explodes. We observed two main dissociation pathways; One pathway is reasonably well understood, and occurs when a soft x-ray ejects an inner valence ($2\sigma_g$ or $2\sigma_u$) electron from the $N_2$ molecule. The second dissociation pathway occurs when the soft x-ray removes an outer valence ($3\sigma_g$) electron, and a second electron is simultaneously excited in a process known as electron shakeup. These shakeup states in molecules have interesting features and fragmentation dynamics that have not been previously explored either theoretically or experimentally. We can follow the dynamics of these shakeup states as the molecule dissociates by using a short IR probe pulse to further ionize the excited $N_2^+$ to the $N_2^{2+}$ ground state, forming two $N^+$ fragments. The reaction microscope then allows us to detect the kinetic energy of the coincident $N^+/N^+$ ion pair as

a function of time delay to follow the dissociation dynamics. Our soft x-ray pump–IR probe scheme thus makes it possible to map the electronic and nuclear dynamics of highly excited $N_2^+$ states with femtosecond time resolution and angstrom spatial resolution. By a comparison of these measurements with theoretical calculations, our results suggest that this fragmentation occurs predominantly via an antibonding shakeup state, where a loosely bound $4\sigma_u$ electron surrounds an exploding $N_2^{2+}$ core. The loosely bound shakeup electron experiences a rapid transition from a nearly spherically symmetric initial molecular potential to a two-center potential and finally to a separate atom and ion at the dissociation limit. Furthermore, our data show evidence of three-body dynamics and quantum interferences resulting from the two-center nature of the molecular potential (*20*).

We generated high-harmonic light in a phase-matched geometry (*21*) by upshifting intense 2-mJ, 28-fs pulses centered at 800 nm from a 2-kHz ultrafast Ti:sapphire laser system (KMLabs, Boulder, CO) in a 2.5-cm-long, 150-μm-diameter hollow waveguide filled with Ar gas. The peak laser intensity in the waveguide was ~$10^{14}$ W cm$^{-2}$, and the argon pressure was typically 30 torr. A single harmonic order at a wavelength of 30 nm was selected from the comb of odd harmonics emerging from the waveguide and focused to ~100 μm with two multilayer mirrors. This resulted in a pump beam of ~43-eV photon energy with a few–electron volt bandwidth, a pulse duration of ~5 fs, and a flux of ~$10^6$ photons per pulse or $2 \times 10^9$ photons/s. Part of the laser output was split, delayed, and then recombined with the soft x-ray pump beam to serve as a colinear probe beam. The probe beam was focused using a 75-cm lens to a ~100-μm-diameter spot with an intensity of ~$10^{12}$ to $10^{13}$ W cm$^{-2}$. The $N_2$ gas was cooled and confined using a supersonic jet expansion employing a 30-μm nozzle. The cold supersonic part of the jet was selected with a 300-μm skimmer placed ~8 mm from the gas nozzle. The gas density in the interaction region was estimated to be $10^{11}$ molecules/cm$^{-3}$. This experimental setup was run continuously with excellent stability and minimal loss in detector count rate for data-acquisition times of >100 hours.

The reaction microscope consists of an electrode configuration that generates a uniform electric field in the interaction region to accelerate reaction fragments toward the detectors. A magnetic field was also used to confine the fast-moving electrons. The result was near-4π collection efficiency for both electrons and ions. The fragments were then detected by microchannel plates employing a position-sensitive delay-line anode (RoentDek, Kelkheim-Ruppertshain, Germany). These detectors record the position coordinates and time of flight of the fragments with spatial and temporal resolutions of ~100 μm and 500 ps, respectively. Together with the knowledge of the initial position of the reaction (defined by the interaction region) and the electric and magnetic fields, this information enables the reconstruction of all three components of momentum of each particle that hits a detector. Using this reaction-imaging apparatus, we accumulated electron and ion data for each laser shot. Post analysis of the data was then used to deduce electron-ion correlations and to implement coincidence conditions that filter the data to identify the different dissociation channels.

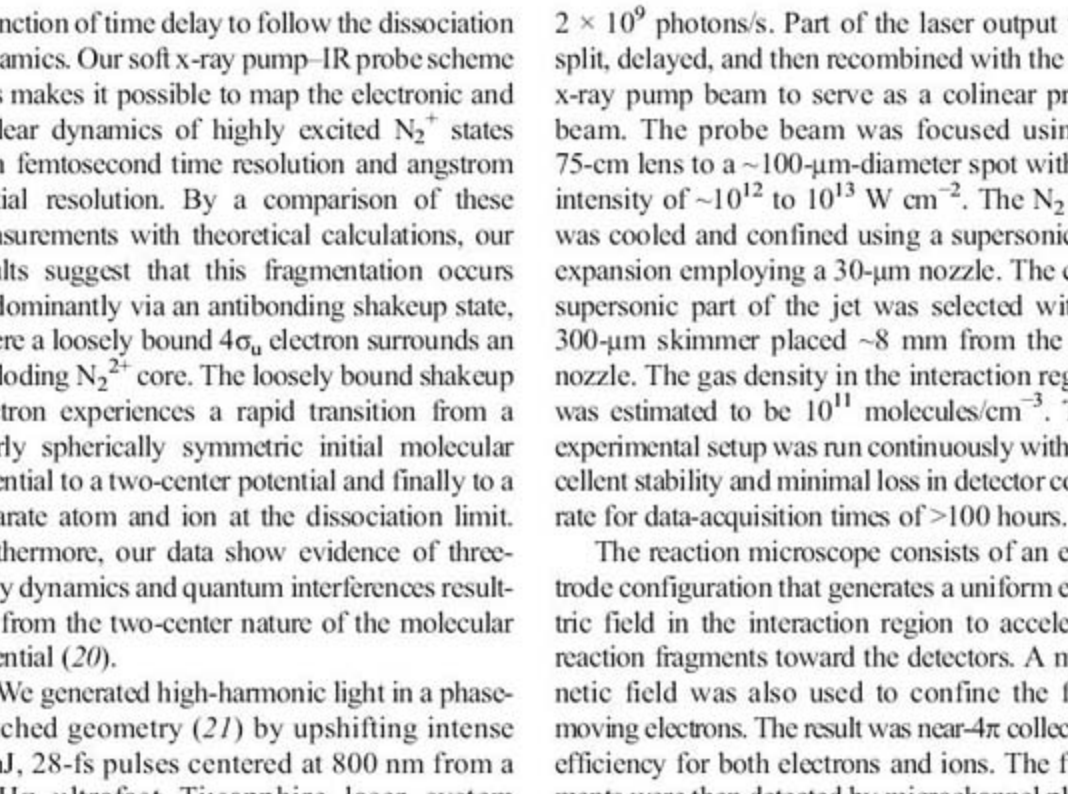


**Fig. 1.** (**A**) Experimental setup to probe radiation-induced dynamics. High-harmonic pulses centered at 43 eV are generated in a waveguide to serve as the pump beam. An IR laser beam serves as the probe. HHG, high-harmonic generation. (**B**) Spectrum of the soft x-ray pulse after reflection from two multilayer mirrors. (**C**) Inside the reaction microscope. After the soft x-rays interact with a supersonic $N_2$ gas jet, uniform electric (*E*) and magnetic (*B*) fields guide the reaction fragments to position-sensitive detectors. The combined position and time-of-flight information yields the vector momentum ($\vec{p}$) of each fragment in coincidence. (**D**) Exterior schematic of the reaction microscope.

The photoionization of $N_2$ by x-rays can initiate a series of complex molecular processes. The ground-state configuration of $N_2$ is $1\sigma_g^2 1\sigma_u^2 2\sigma_g^2 2\sigma_u^2 1\pi_u^4 3\sigma_g^2$, and our photon energy of 43 eV can remove both outer valence ($1\pi_u^4 3\sigma_g^2$) and inner valence ($2\sigma_g^2 2\sigma_u^2$) electrons. The inner-valence ionization pathway (schematically shown in blue in Fig. 2A) results in the formation of many highly excited ion states ($N_2^{+*}$), with potential energies typically between 23 and 43 eV (relative to the $N_2$ ground state) (*22*). The cross sections for forming these states are known from synchrotron measurements (*23*). The finite bandwidth of our photon source does not allow us to resolve each state separately; however, previous work (*22*, *24*–*26*) indicates that most of these inner-valence ionized molecules rapidly evolve to separated $N(2s^2 2p^3)$ and $N^+(2s^2 2p^2)$ fragments (i.e., electronic states with principal quantum number $n = 2$) (*27*). These dissociation channels are schematically represented by potential-energy curves that lie in the blue band shown in Fig. 2B.

Figure 2C plots ion- and electron-energy correlation map obtained for coincident fragments using the reaction microscope. We can identify the known dissociation pathways resulting from inner-valence ionization of the molecule using energy conservation: $E_{e^-} + 2E_{N^+} = h\omega_{x\text{-}ray} - E_{limit}$, in which the sum of the fragment kinetic energies [electron ($E_{e^-}$) and ion ($E_{N^+}$) + neutral] is equal to the soft x-ray photon energy ($h\omega_{x\text{-}ray}$) minus the energy corresponding to the dissociation limit ($E_{limit}$). Our data confirm that inner-valence hole states of the molecule decay to the $n = 2$ dissociation limit (events that lie between the blue lines in Fig. 2C) through channels that are indicated in Fig. 2B. The horizontal substructure at 14 eV of electron energy and 1 eV of ion energy is due to dissociation from inner-valence ionic states that lie in the range of 27 to 31 eV (*28*). This well-defined feature has also been observed in other studies as the F-band (*25*, *26*).

Dissociation pathways that yield both a low-energy electron and a low-energy ion (indicated by events between the red lines in Fig. 2C) and that represent a very large fraction of dissociation events cannot be explained by the dissociation of inner-valence hole states. From energy-conservation arguments, these channels must represent a molecular excitation near the double-ionization threshold (~43 eV) that dissociates to a ground-state ion and an excited neutral atom, with the outer electron in an $n = 3$ principal quantum number state (red band in Fig. 2B). These pathways have not been investigated previously. We show below that these dissociation channels are consistent with fragmentation of excited states resulting from an electron-shakeup process (Fig. 2A) accompanying outer-valence $3\sigma_g$ ionization.

To follow the time evolution of these shakeup states as they dissociate, as well as to uniquely identify them, we used a time-delayed IR probe pulse to eject a second electron from the molecule by multiphoton ionization. This second ionization step promotes the excited molecular ion ($N_2^{+*}$) to the doubly ionized ($N_2^{2+}$) ground state, which then explodes into two $N^+$ ions of equal and opposite momentum (*29*). The signature of this final product channel can be isolated from the data very effectively by detecting two $N^+$ ions in coincidence that have zero total momentum in the center-of-mass frame. Because we do not observe any counts in the correlated $N^+/N^+$ product channel in the absence of the IR field, we can cleanly probe the evolution of the $N_2^{+*}$ dissociating wave packet, free of background contamination from other $N^+$ ions. By varying the pump-probe time delay, we interrupt the fragmentation of the $N_2^{+*}$ at different times (i.e., different internuclear separations) (Fig. 3A). Using the reaction microscope to monitor $N^+/N^+$ coincidences, we can map the ion kinetic energy release (KER) as a function of time delay. The ion KER at any given time delay $t$ between the soft x-ray pump and the IR probe is determined by the sum of the energy that the ions gain in the $N_2^{+*}$ state (times $0 \rightarrow t$), as they evolve from the Frank-Condon region toward the dissociation limit, plus the energy gained after time $t$ on the known $N_2^{2+}$ dissociation curve (*30*). In a classical picture, we can thus write the ion KER as Eq. 1

$$KER(t) = [E_1(r_0) - E_1(r_t)] + [E_2(r_t) - E_2(\infty)] \quad (1)$$

where $r_0$ and $r_t$ are the internuclear separations at time delays 0 and $t$, respectively; $E_1$ represents the potential-energy curve for $N_2^{+*}$; and $E_2$ represents that for $N_2^{2+}$. The time-dependent KER data can then be used to deduce the characteristics and dynamics of the unknown excited state(s), namely the $E_1(r)$ curve (Fig. 3A).

We find that near zero time delay between the soft x-ray pump and IR probe, the $N_2^{+*}$ wave packet is instantly transferred to the $N_2^{2+}$ potential-energy curve, leading to a large ion KER from 6 to 8 eV (Fig. 3B). The finite spread of KER data is a direct result of Frank-Condon vibrational spread of the wave packet released on the $N_2^{+*}$ potential. The limiting values of KER are dependent on the exact shape of potential-energy surfaces in the Frank-Condon region, as explained later when we discuss our theoretical calculations. We observed that the ion KER decreases sharply as a function of time delay to ~4 eV within 150 fs. For large pump-probe time delays ≥300 fs, the ion KER does not change appreciably. This indicates that the excited $N_2^{+*}$ has already evolved into two separate noninteracting fragments: a ground-state ion and an excited neutral atom. The low ion KER (~3 eV) at large time delays (internuclear separations) indicates that the states we are probing are highly excited states that, from energy conservation, must decay to the $n = 3$ limit (Fig. 2).

The observed time-resolved KER data can be explained by considering electron-shakeup processes, in which a second electron is simultaneously excited when a $3\sigma_g$ valence-shell electron is ejected by a soft x-ray (red in Fig. 2A). To support this hypothesis, we performed calculations to identify possible candidates for the highly excited $N_2^+$ states that formed as a result of a shakeup process. These states include Rydberg states (*31*) surrounding a doubly charged molecular core, as have been observed in near-threshold photoelectron spectra obtained by Krummacher *et al.* (*22*) in the energy range up to 40 eV. However, with the exception of binding energies, no further information has been reported on these states. Our calculations therefore construct these states to correspond approximately to a doubly ionized ground-state ($N_2^{2+}$) molecular core with an additional excited electron. For a given internuclear separation, we first calculated the effective potential of $N_2^+$ ions in the ground state by the multiple-scattering self-consistent method (*32*). The orbital energy of various excited shakeup states was calculated using an effective potential with a Coulomb tail correction in the asymptotic region. Adding this orbital energy to the ground-state energy of $N_2^{2+}$ (*30*), we obtained the potential-energy curves for the excited shakeup states. (Fig. 4). These states are populated when the electron in a $3\sigma_g$ state is ejected by a 43-eV photon, and a second valence $3\sigma_g$ electron is promoted to the higher valence levels $3\sigma_u$, $4\sigma_u$, $4\sigma_g$, and assorted $\pi$ orbitals. The electron state corresponding to a $4\sigma_u$ shakeup (black curve in Fig. 4) is closest to the $N_2^{2+}$ ground state and has the largest overlap with the valence $3\sigma_g$ orbital. Hence, this state is most likely to be populated in the Frank-Condon region as a result of an electron-shakeup process. This state then decays to the dissociation limit, with the final configuration of fragments corresponding to an ion $N^+$ ($^3P$) and a neutral N atom ($n = 3$).

Choosing this $4\sigma_u$ electron state (Fig. 4) as a likely candidate for $E_1(r)$ in Fig. 3A, we calculated the KER at different stages of fragmentation

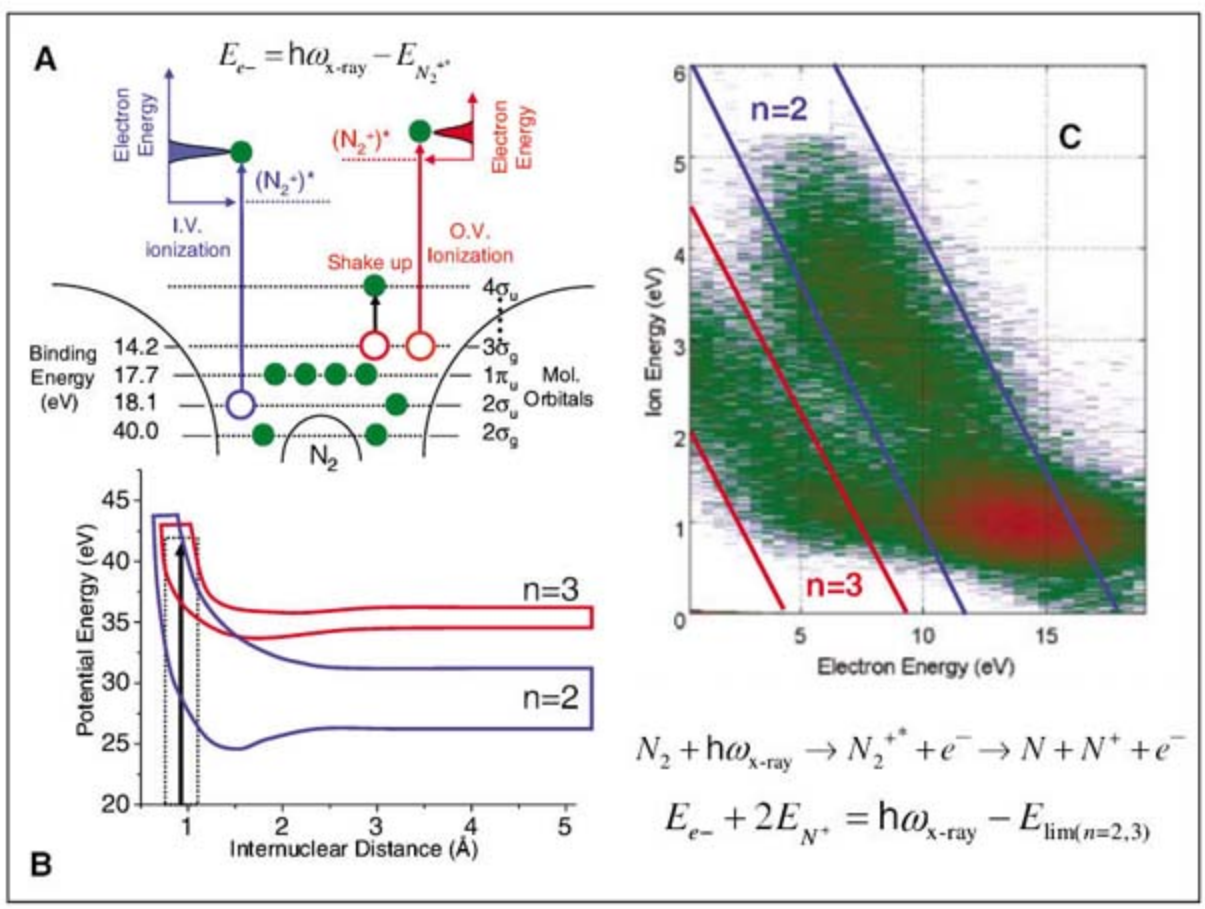


**Fig. 2.** (**A**) Schematic of the formation of highly excited $N_2^+$ through an inner-valence (I.V.) ionization process (blue) or an electron-shakeup process (red) accompanying outer-valence (O.V.) ionization. The electron binding energies are listed on the left, whereas the molecular orbitals are labeled on the right. $E_{e-}$, electron kinetic energy; $\omega_{x\text{-}ray}$, x-ray photon frequency. (**B**) Schematic of the predominant dissociation channels of $N_2^{+*}$, where the inner-valence ionization channel is shown in blue, and the shakeup channel is shown in red. The 43-eV soft x-ray photon (black arrow), Franck Condon excitation region (dotted rectangle) and dissociation limits (atomic states $n$ = 2, 3) are indicated. Å, angstroms. (**C**) Recoil and electron-energy correlation diagram for the dissociation of $N_2$ initiated by an ultrafast soft x-ray pulse. $e^-$, electron.

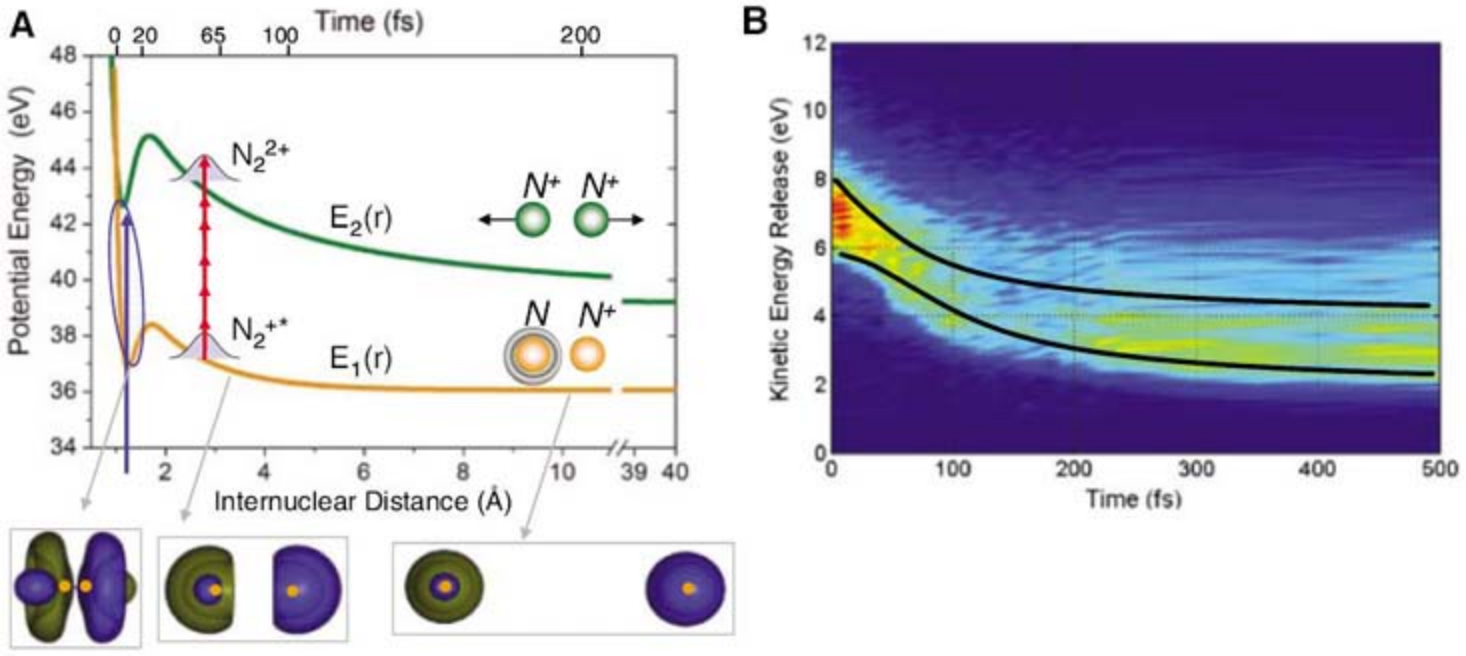


**Fig. 3.** (**A**) A soft x-ray pump pulse photoionizes $N_2$ to a highly excited $N_2^{+*}$ shakeup state [orange curve labeled $E_1(r)$]. The probe IR pulse further ionizes $N_2^{+*}$ to the final $N_2^{2+}$ ground state, shown in green and labeled $E_2(r)$. The $N_2^{2+}$ potential curve was adapted from (*30*), whereas the $N_2^{+*}$ curve was calculated as described in the text. A schematic of the wave function for the $N_2^{+*}$ state is also shown at different internuclear separations. (**B**) Evolution of the ion KER in the $N^+/N^+$ channel as a function of time delay between the 5-fs soft x-ray pump pulse and the IR probe pulse. The experimental data were not normalized for the long-term drift in EUV flux levels of 15% over a 2-day time period. The theoretically calculated KER for the $4\sigma_u$ electron shakeup is plotted as a band. The lower limit for this band is imposed by the local potential minimum of the $N_2^{+*}$ and also by the potential barrier of the $N_2^{2+}$ state for time delays near zero. The upper limit is set by the width of the $N_2$ ground-state wave packet, i.e., the width of the Frank Condon region [blue region of the $E_1(r)$ curve in (A)].

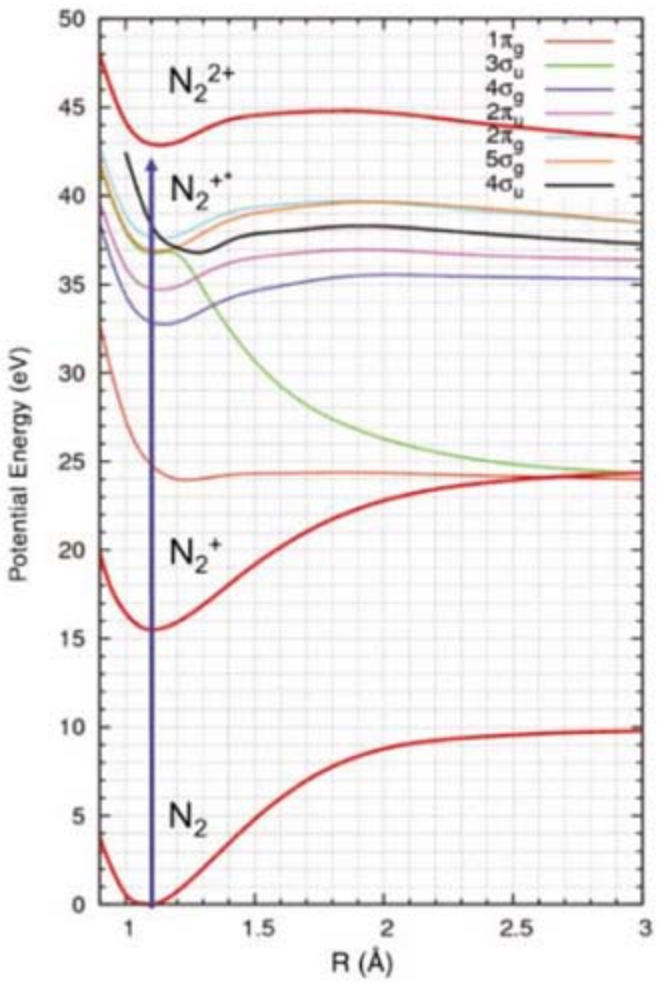


**Fig. 4.** Calculated $N_2^{+*}$ states resulting from an electron-shakeup process. These states consist of a loosely bound electron surrounding a doubly charged $N_2^{2+}$ core. The black curve corresponding to the $4\sigma_u$ electron shakeup is predominantly populated because of the large overlap with the valence orbital. This shakeup state corresponds to the excited state $E_1(r)$ (shown in Fig. 3A). It was also used to calculate the theoretical KER band (shown in black in Fig. 3B).

using Eq. 1 and the derivative in Eq. 2 (where $\mu$ is the reduced mass)

$$dr_t/dt = \sqrt{2[E_1(r_0) - E_1(r_t)]/\mu} \qquad (2)$$

The $N^+/N^+$ KER data obtained from theory is in the form of a band of finite width, and the two limits are overlaid as black lines on the experimental data in Fig. 3B. These KER limits correspond to two limiting values of the radius of the $N_2^{+*}$ wave packet launched by soft x-ray excitation (Fig. 3A). The slope of the $N_2^{+*}$ potential in the Frank-Condon region implies that excitation at smaller internuclear distances leads to higher KER. The upper limit of the KER is thus set by the width of the parent $N_2$ ground-state wave packet. The lower limit is imposed by the condition that the wave packet has to overcome the local potential minimum on the $N_2^{+*}$ potential, as well as the potential barrier of $N_2^{2+}$ for time delays near zero (Fig. 3A). These restrictions lead to the distinctive KER spectra shown in Fig. 3B. The excellent agreement between theory and experiment in Fig. 3B demonstrates that the $4\sigma_u$ orbital, because of its large overlap with the valence shell, is a major excitation and fragmentation channel for soft x-ray excited $N_2$ molecules. This dissociation channel and its dynamics have not been yet identified or explored.

Next, we interpreted the finer features of the shakeup-state dissociation dynamics. As the internuclear distance increases, there is a sharp decrease in KER over the first 150 fs (Fig. 3B). The internuclear distances corresponding to the transition region between 50 and 150 fs range from ~2 to 6 Å. (From Eq. 2 we can relate time and distance, and both are labeled in Fig. 3A.) This transition represents a rapid change from an almost spherically symmetric initial binding potential for the outer excited electron to a final two-center potential at larger internuclear distances. In terms of the internuclear potential, the molecule transitions from an almost purely repulsive interaction between two charged $N^+$ cores (where the excited electron does not play a strong role) to a regime in which the excited electron screens the Coulomb repulsion between the two $N^+$ cores. This transition can be seen as a change in the wave function for the antibonding $4\sigma_u$ orbital (Fig. 3A). At $r = 1.1$ Å, there is almost no electron density between the two nuclei (orange in Fig. 3A). However, at separations >3 Å, the electron density between two nuclei is substantial, and the two-center nature of the potential is apparent. Past this transition region, the excited-state potential-energy curve is essentially flat, which reflects the loss of the long-range $1/r$ Coulomb repulsion between two cores as one of the partners becomes uncharged. For times >150 fs, the KER

data exhibit a complex structure suggestive of two-center quantum interferences. These rapid electronic dynamics will be an interesting topic for further study.

In the future, this work can be extended to a range of atomic and molecular systems to explore complex, correlated electron dynamics and highly excited states. Interesting topics such as the attosecond dynamics of electron transitions, the observation of ultrafast electron transfer in molecules, and the influence of molecular structure on these x-ray driven dynamics are challenging problems that are now accessible with the use of the techniques illustrated here.

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23. Using 43.2-eV photons from a synchrotron, the partial cross section for inner-valence ionized states between 23 and 43 eV was measured to be 33% of the total photoionzation cross section (*22*).
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27. Some examples of such dissociation limits are (N, N$^+$) = ($^3$P, $^2$P$_0$), ($^1$S, $^4$S$_0$), ($^1$D,$^2$D$_0$), and ($^1$D, $^2$P$_0$).
28. This strong feature is probably due to the concentration of the $^2\Sigma_g^+$ oscillator strength in the region ranging from 27 to 31 eV (F-band). Dissociation from this band gives rise to a quasi-monoenergetic photoelectron peak, with a corresponding well-defined KER. The observed electron-energy width results from the soft x-ray pulse bandwidth.
29. We identify and distinguish bound and dissociative channels in the supporting online material. The triple coincidence data presented in fig. S1 confirms that we selectively probed highly excited dissociative states near the double-ionization threshold of $N_2$.
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### Supporting Online Material

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# A Basal Dromaeosaurid and Size Evolution Preceding Avian Flight

**Alan H. Turner,[1]* Diego Pol,[2] Julia A. Clarke,[3,4,1] Gregory M. Erickson,[5] Mark A. Norell[1]**

**Fossil evidence for changes in dinosaurs near the lineage leading to birds and the origin of flight has been sparse. A dinosaur from Mongolia represents the basal divergence within Dromaeosauridae. The taxon's small body size and phylogenetic position imply that extreme miniaturization was ancestral for Paraves (the clade including Avialae, Troodontidae, and Dromaeosauridae), phylogenetically earlier than where flight evolution is strongly inferred. In contrast to the sustained small body sizes among avialans throughout the Cretaceous Period, the two dinosaurian lineages most closely related to birds, dromaeosaurids and troodontids, underwent four independent events of gigantism, and in some lineages size increased by nearly three orders of magnitude. Thus, change in theropod body size leading to flight's origin was not unidirectional.**

Which nonflying maniraptoran dinosaurs are the closest relatives to birds (Avialae) has been debated (*1*–*5*). Dromaeosaurids and troodontids are the two clades consistently found to be most closely related to avialans (*1*–*8*). Discoveries of these dinosaurs, which illuminate the features ancestrally present in the first flighted theropods, have remained rare. Here we report a basal dromaeosaurid theropod: Theropoda Marsh, 1884; Maniraptora Gauthier, 1986; Paraves Sereno, 1997; Dromaeosauridae Matthew and Brown, 1922; *Mahakala omnogovae*, new taxon. The new taxon is small (~70 cm long) and possesses features absent in other dromaeosaurids but shared with early troodontids and avialans.

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**Holotype.** Specimen number IGM (Mongolian Institute of Geology, Ulanbaatar) 100/1033, a partial skull and postcranial skeleton (Figs. 1 and 2).

**Etymology.** "Mahakala," Sanskrit for one of the eight protector deities (dharmapalas) in Tibetan Buddhism. The specific epithet refers to the southern Gobi provenance of this taxon.

**Locality and horizon.** The Tugrugyin Member of the Djadokhta Formation (Campanian) (*9*, *10*), Tugrugyin Shireh, Ömnögov, Mongolia (*10*, *11*).

**Diagnosis.** A small paravian diagnosed by the following combination of characters (autapomorphies are noted by *): a strongly compressed and anteroposteriorly broad ulna tapering posteriorly to a narrow edge*; an elongate lateral crest on the posterodistal part of the femur*; anterior caudal vertebrae with subhorizontal, laterally directed prezygapophyses*; a prominent supratrochanteric process; and the absence of a cuppedicus fossa.

Estimated at 70 cm long, *Mahakala* is similar in size to the basal avialan *Archaeopteryx* and basal members of other maniraptoran clades such as the oviraptorosaur *Caudipteryx* and the troodontid *Mei long*. The specimen is a young adult or near adult, based on the degree of neurocentral and astragalocalcaneal fusion, braincase coossification, and histological analysis (fig. S4). Thus, it can be distinguished from the contemporaneous *Archaeornithoides*, which is of similar size but is a juvenile (*12*).

The braincase, quadrate, and frontals are well preserved. Unlike dromaeosaurids but similar to troodontids such as *Sinovenator* (*7*) and *Mei* (*8*), the frontals are dorsoventrally vaulted and the interorbital region is narrow, indicating proportionally large orbits. The anterolateral corner of the frontal lacks the articulation notch present in other dromaeosaurids. The frontals transition smoothly from the orbital margin to the postorbital processes as in troodontids (*13*), but unlike the abrupt transition and sharply demarcated postorbital processes of dromaeosaurids. The supratemporal fossa margin is weakly curved, not sinuous as in all other dromaeosaurids except *Tsaagan* (*5*) and *Dromaeosaurus* [AMNH (American Museum of Natural History) FR

5356]. The quadrate is incipiently bistylic, unlike the single-headed ball-shaped process in other dromaeosaurids. A depression on the prootic may correspond to a secondary articulation surface for the quadrate. This depression corresponds topographically to the braincase articulation facet in birds and alvarezsaurids but is also present in the troodontid *Byronosaurus* (*14*). The lateral braincase wall lacks any indication of a well-developed otosphenoidal crest like that in troodontids (*14*). The paroccipital processes are relatively short and distally twisted rostrolaterally as in other dromaeosaurids.

The axis bears a single pneumatic opening and has small epipophyses that do not overhang the postzygapophyses. The sacrum comprises six apneumatic, coossified centra as in *Rahonavis* and mature specimens of *Velociraptor* (IGM 100/986 and IGM 100/985). The fused neural arches of the posterior sacral vertebrae form a bony lamina as in other dromaeosaurids. The tail is long as in basal avialans (such as *Archaeopteryx* and *Jeholornis*), basal troodontids (such as *Jinfengopteryx* and *Mei*), and other dromaeosaurids. The transition point occurs between caudals (Cd's) 11 and 12 and is more posteriorly located than in *Rahonavis* (proximal to Cd 9) or *Velociraptor* (proximal to Cd 10). The distal caudal postzygapophyses are smaller than the prezygapophyses. As in to other basal paravians, the postzygapophyses do not exceed the posterior margin of the vertebral centra. The lateral surface of the proximal caudals bears a low ridge similar

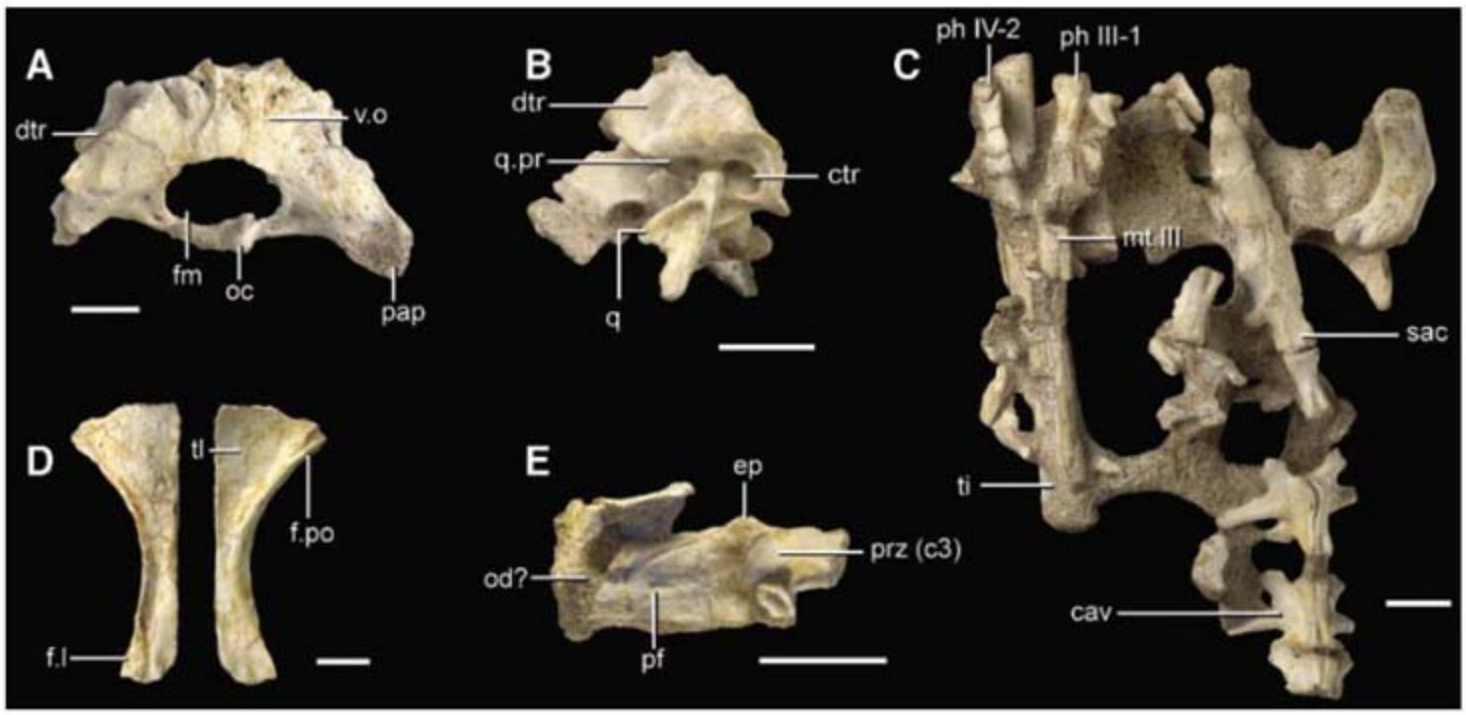


**Fig. 1.** *Mahakala omnogovae* IGM 100/1033, holotype. (**A**) Skull in occipital view. (**B**) Braincase in left lateral view. (**C**) Sacrum and partial right leg in ventral view. (**D**) Frontal in dorsal (left) and ventral (right) views. (**E**) Axis vertebra in left lateral view. Scale bars, 5 mm in (A), (B), (D), and E) and 1 cm in (C). Abbreviations are as follows: cav, caudal vertebra; ctr, caudal tympanic recess; dtr, dorsal tympanic recess; ep, epipophysis; f.l, lacrimal facet; f.po, postorbital facet; fm, foramen magnum; mt, metatarsus; oc, occipital condyle; od, odontoid; pap, paroccipital process; pf, pneumatic foramen; ph, phalanx; prz, prezygapophysis; q.pr, contact surface on prootic for quadrate; q, quadrate; ti, tibia; tl, tectal lobe; sac, sacrum; v.o, occipital vein track.

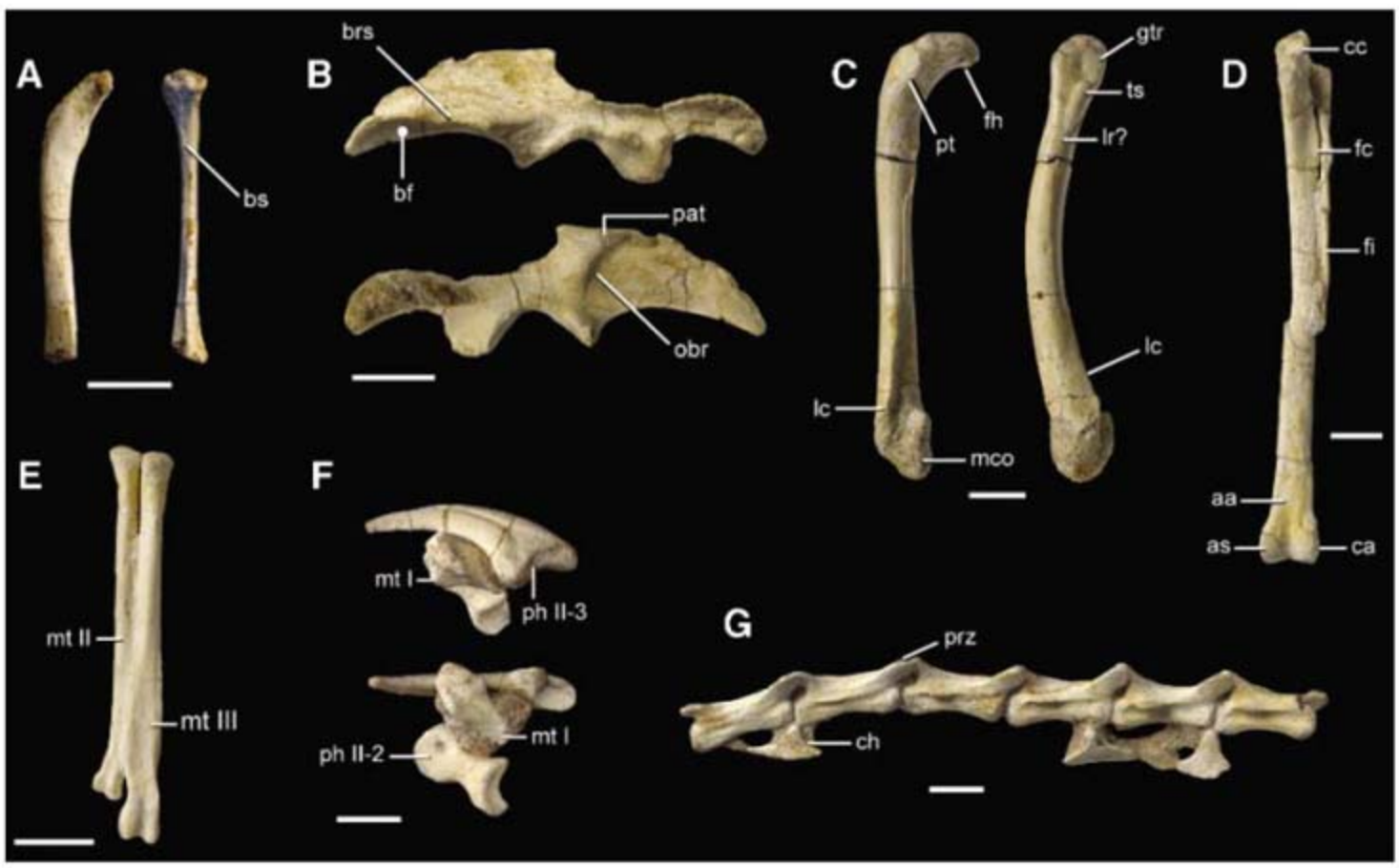


**Fig. 2.** *Mahakala omnogovae* IGM 100/1033, holotype. (**A**) Right ulna in lateral (right) and medial (left) views. (**B**) Ilium in medial (top) and lateral (bottom) views. (**C**) Femur in posterior (left) and lateral (right) views. (**D**) Tibia in anterior view. (**E**) Left metatarsus in anterior view. (**F**) Right raptorial claw. (**G**) Midcaudal vertebrae. Scale bars, 1 cm in (B) to (E) and 5 mm in (A), (F), and (G). Abbreviations are as follows: aa, ascending process of astragalus; as, astragalus; bf, brevis fossa; brs, brevis shelf; bs, biccipital scar; ca, calcaneum; cc, cnemial crest; ch, chevron; fc, fibular crest; fi, fibula; gtr, greater trochanter; lr, lateral ridge; lc, lateral crest; mco, medial condyle; mt, metatarsal; obr, oblique ridge; pat, posterior antitrochanter; prz, prezygapophysis; pt, posterior trochanter; ts, trochanteric shelf.

to that in *Buitreraptor* (*4*) and *Rahonavis* [UA (University of Antananarivo) 8656]. The chevrons in *Mahakala* are platelike as in many derived coelurosaurs.

The scapula is narrow and straplike and has a strongly compressed ovoid cross section. The preserved portion of the incomplete humerus suggests that the entire humerus was reduced in contrast to the condition of most coelurosaurs. The ulna is distinctly bowed as in most maniraptorans (*1*) but is strongly compressed and possesses a small biceps tubercle. The distal region of the radius is expanded and flattened as in paravians (*11*). A semilunate carpal covers the proximal surfaces of metacarpals I and II; a plesiomorphic conformation lost in most avialans.

The ilium is dolichoiliac. A prominent supratrochanteric process is present as in *Unenlagia*, *Rahonavis*, and many avialans. The brevis shelf is triangular and does not extend laterally as in some other basal dromaeosaurids. No antiliac shelf is present, therefore *Mahakala* lacks a defined cuppedicus fossa—an absence unique within dromaeosaurids but characteristic of avialans such as *Apsaravis* (*15*) and *Yixianornis* (*16*).

The femur is anteriorly bowed. The lesser trochanter is well developed, and its anterior edge is continuous with the greater trochanter. The fourth trochanter is present as a smooth and weakly developed ridge. Unlike *Velociraptor* (IGM 100/986), the lateral ridge is poorly developed, and the moundlike trochanteric shelf is proximodistally elongated and closely connected to the posterior trochanter. A prominent crest extends from the distal third of the shaft to the ectocondylar tubercle. The tibia is longer than the femur and possesses a single cnemial crest. The lateral surface of the calcaneum is distinctly concave and lacks the notch for the articulation with the distal fibula that is present in dromaeosaurids and other nonavian theropods. This condition is shared with *Rahonavis*, basal avialans

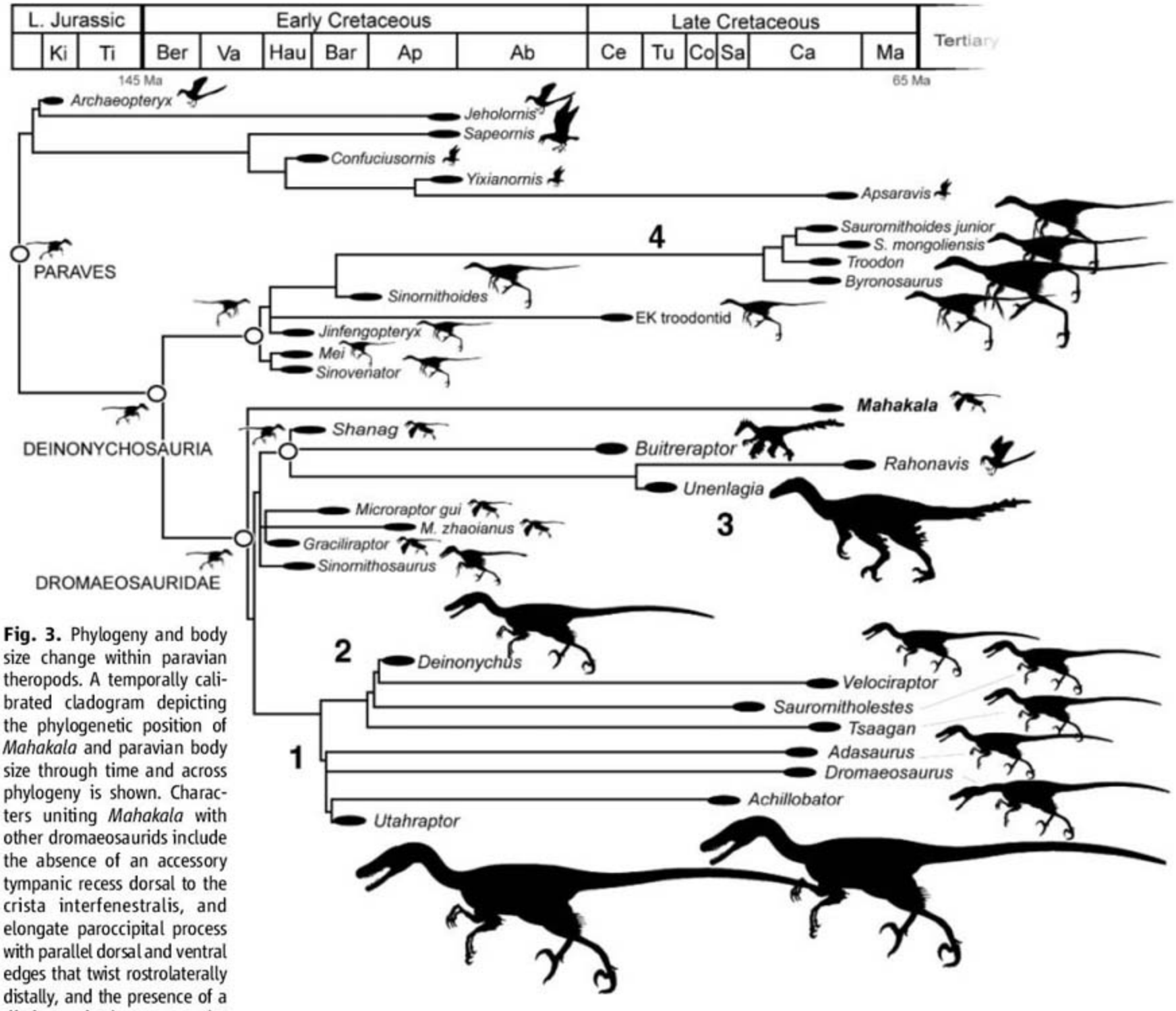


**Fig. 3.** Phylogeny and body size change within paravian theropods. A temporally calibrated cladogram depicting the phylogenetic position of *Mahakala* and paravian body size through time and across phylogeny is shown. Characters uniting *Mahakala* with other dromaeosaurids include the absence of an accessory tympanic recess dorsal to the crista interfenestralis, and elongate paroccipital process with parallel dorsal and ventral edges that twist rostrolaterally distally, and the presence of a distinct ginglymus on the distal end of metatarsal II (*17*). Silhouettes are to scale, illustrating the relative magnitude of body size differences. Left-facing silhouettes near open circles show reconstructed ancestral body sizes. Ancestral paravian body size is estimated to be 600 to 700 g and 64 to 70 cm long (*17*). The ancestral deinonychosaur, troodontid, and dromaeosaurid body size is estimated at ~700 g. Large numbers (1, 2, 3, and 4) indicate the four major body increase trends in Deinonychosauria. See the supporting online material for further ancestral body size reconstruction data. Ma, Maastrichtian; Ca, Campanian; Sa, Santonian; Co, Coniacian; Tu, Turonian; Ce, Cenomanian; Ab, Albian; Ap, Aptian; Bar, Barremian; Hau, Hauterivian; Va, Valanginian; Ber, Berriasian; Ti, Tithonian; Ki, Kimmeridgian. Ma, million years ago.

(*2*), and derived alvarezsaurids. Unlike most troodontids and microraptorines, but similar to *Archaeopteryx* and derived dromaeosaurids, the foot of *Mahakala* exhibits the plesiomorphic unconstricted condition for metatarsal III, further indicating that this avian trait may be the primitive condition for paravians. The distal end of metatarsal II is composed of an asymmetrical ginglymoid articular surface and phalanx II-2 has a well-developed proximal heel and hypertrophied ginglymoid trochlea. This suite of characters is present only in dromaeosaurids.

Phylogenetic analysis identifies *Mahakala* as a basal dromaeosaurid and supports paravian monophyly with birds (Avialae) as the sister group to a monophyletic Deinonychosauria (Dromaeosauridae + Troodontidae) (Fig. 3 and fig. S1). Although discovered in relatively young Cretaceous deposits, the basal position of *Mahakala* has several implications regarding our understanding of the early history of deinonychosaurians (*17*). First, *Shanag* from the Early Cretaceous of Mongolia (*18*) nests within the purported Gondwanan lineage of dromaeosaurids, Unenlagiinae. This topology complicates recently proposed vicariance-driven origin hypotheses for these groups (*4*, *19*). Second, these dinosaurs are united with Jehol microraptorines (*Microraptor*, *Graciliraptor*, and *Sinornithosaurus*) to form the sister group to derived dromaeosaurids from Laurasia (velociraptorines and allied forms). Third, the purported avialan *Jinfengopteryx* (*20*) is a troodontid. *Jinfengopteryx* has feathers; it thus demonstrates the presence of feathers of modern aspect in a troodontid.

Decrease in body size is a trend in coelurosaurs (*3*, *8*, *21*) and is thought to have played an important role in the origin of birds and flight (*6*, *11*, *22*–*24*). Dromaeosaurids and other coelurosaurs, however, may have undergone clade-specific increases in body size (*8*, *25*). Testing these trends requires empirical size reconstructions for each node of the coelurosaur tree. We estimated ancestral body sizes for each internal node (ancestral node) using body mass estimates from femoral length measurements. These data were treated as a continuous additive trait and optimized across the phylogeny (*16*).

Our analysis (fig. S2) indicates that small body size was not a derived condition at *Archaeopteryx* or Avialae, where flight evolution in theropods is currently inferred. The ancestral dromaeosaurid, troodontid, and deinonychosaurian are reconstructed as small, each with a body mass around 700 g (Fig. 3). The basal members of these lineages are the same size as the early avialan *Jeholornis*. Additionally, our results indicate that deinonychosaurs underwent four parallel trends of body size increase. Three of these events occurred within Dromaeosauridae: *Deinonychus* increased in size by more than two orders of magnitude, as did *Unenlagia*, and the *Achillobator* + *Utahraptor* clade increased by three orders of magnitude. A single trend of body size increase was observed in troodontid body size. These events were contemporaneous with a decrease in avialan body sizes. Our analysis implies that the ancestral paravian had a body size of 600 to 700 g and was ~65 cm long, roughly the size of the largest specimens of *Archaeopteryx* or *Sapeornis* and entailing the size range reconstructed for basal deinonychosaurs. Thus, miniaturization preceded the avialan node and the origin of flight, and as a result, hypotheses relating ontogenetic or metabolic controls on miniaturization to flight origin in theropods must be equally capable of explaining the size reduction within ancestral paravians and the iterative trends of size increase in deinonychosaurs.

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### Supporting Online Material

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# 20th-Century Industrial Black Carbon Emissions Altered Arctic Climate Forcing

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Black carbon (BC) from biomass and fossil fuel combustion alters chemical and physical properties of the atmosphere and snow albedo, yet little is known about its emission or deposition histories. Measurements of BC, vanillic acid, and non–sea-salt sulfur in ice cores indicate that sources and concentrations of BC in Greenland precipitation varied greatly since 1788 as a result of boreal forest fires and industrial activities. Beginning about 1850, industrial emissions resulted in a sevenfold increase in ice-core BC concentrations, with most change occurring in winter. BC concentrations after about 1951 were lower but increasing. At its maximum from 1906 to 1910, estimated surface climate forcing in early summer from BC in Arctic snow was about 3 watts per square meter, which is eight times the typical preindustrial forcing value.

Emissions of black carbon (BC) particles result from incomplete combustion during the burning of biomass and fossil fuels (*1*). In the atmosphere, the absorption of sunlight by BC contributes to global warming and alters cloud-formation processes (*2*). Arctic climate is especially vulnerable to BC deposition because of its impact on the albedo of snow, glaciers, and sea ice—accelerating melting and increasing sensitivity to warming (*3*). Despite its importance, little is known about past natural or anthropogenic emissions of BC and its deposition. Glaciers and ice sheets contain a historical record of atmospheric deposition of aerosol-borne chemicals derived from natural and anthropogenic burning. We used measurements

of central Greenland ice cores to assess the origin and climate forcing of BC in snow during the past 215 years. Vanillic acid (VA) and non–sea-salt sulfur (nss-S) were used as indicators of forest fires and industrial pollution, respectively.

We used continuous melter analyses of BC, VA, a wide range of trace elements, and hydrogen peroxide (*4*–*6*). BC was analyzed with a laser-based atmospheric analyzer and VA with electrospray triple-quadrupole mass spectrometry (*6*). Measurements were made on an ice core collected in 2003 from a high-snowfall region of west central Greenland, the D4 site (*6*). Using the known midwinter minimum of hydrogen peroxide concentration in Greenland snow (*7*) and assuming uniform snowfall rate within each year (*6*), we determined monthly and annual BC concentration in Greenland from 1788 through 2002 (Fig. 1A).

BC concentrations varied significantly during the past 215 years and were highly seasonal, particularly during the period before industrialization, beginning in the mid-1800s (Fig. 1A) (*6*). Average preindustrial annual BC concentration was 1.7 ng $g^{-1}$, with generally consistent low winter (defined as December through May) concentrations averaging 1.3 ng $g^{-1}$ and highly variable summer (defined as June through November) concentrations averaging 2.0 ng $g^{-1}$. After 1850, annual BC concentrations began a gradual rise, followed by a rapid increase in ~1888. Annual average concentrations reached a peak of >12.5 ng $g^{-1}$ in 1908 before beginning a general, although erratic, decline through the late 1940s followed by a sharp drop in 1952. Maximum winter BC concentration peaked in 1908 at more than 20 ng $g^{-1}$, with an average wintertime concentration of ~13 ng $g^{-1}$ during the highest 5-year period (1906 through 1910), which is about 10 times the mean winter concentration of 1.3 ng $g^{-1}$ before 1850. During the period from 1851 to 1951, annual average concentrations were 4.0 ng $g^{-1}$, with mean winter and summer concentrations of 4.1 and 3.9 ng $g^{-1}$, respectively. From 1952 to 2002, average annual concentrations were 2.3 ng $g^{-1}$ and were characterized by high year-to-year variability in summer and a gradual decline in winter BC concentrations through the end of the century (Fig. 1B). Although highly variable with season and year, monthly BC concentrations during the late 20th century (Fig. 1A) ranged from <1 ng $g^{-1}$ to >10 ng $g^{-1}$ and are in general agreement with published measurements of BC in Greenland snow (*8*–*11*).

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Although changes in BC measured in the D4 ice core are substantial, it is unclear from a single ice-core record whether the observed changes are representative of central Greenland or the larger Arctic region. As a first step in determining this, we made similar, although discontinuous, measurements from a second ice core collected at the D5 site, ~350 km to the south of D4 (*6*). Changes in BC during the past two centuries (Fig. 1B) were similar at both sites (*6*), suggesting that many of the large summer increases associated with boreal forest fires before industrialization, and the marked increases in winter and spring BC during and after industrialization, were regional and represent central Greenland and possibly much of the Arctic, including the seasonally snow-covered regions of northern and eastern Canada and sea-ice–covered areas of the North Atlantic.

To investigate BC sources in the Greenland records, we used ice-core measurements (*6*) of the conifer-specific forest fire indicator VA (*12*, *13*) and measurements of nss-S as an indicator of industrial emissions (mostly from fossil fuel combustion) (*6*, *14*).

Comparisons of annual average BC and VA concentrations suggest that conifer combustion was the major source of BC in Greenland before 1850 (Fig. 2A) and a significant source during summer throughout the 215-year record. Before 1850, variations in BC concentrations closely matched changes in VA concentrations. Correlations between annual, winter, and summer concentrations of VA and BC were 0.87, 0.72, and 0.87 ($P < 0.0001$), respectively. During the period from 1850 to 1951, correspondence between VA and BC concentration dropped dramatically, particularly in winter. Although correlations between annual and summer average concentrations remained significant (annual: $r = 0.56$, $P < 0.0001$; summer: $r = 0.34$, $P < 0.0005$), winter concentrations showed no covariance. From 1951 to 2002, winter concentrations also were uncorrelated, whereas the correlation in summer concentrations remained at 0.44 ($P < 0.0008$).

Air-mass back-trajectory modeling suggests that the eastern and northern United States and Canada are likely source regions of BC measured at the D4 ice-core site (*6*). We used the National Oceanic and Atmospheric Administration Climate Monitoring and Diagnostics Laboratory atmospheric trajectory model (*15*), driven by velocity fields from the ERA-40 reanalysis for 1958 through 2002 (*16*). Modeling suggests that most BC is wet-deposited and has an atmospheric lifetime of ~3 days (*11*), so we used 3-day trajectories corresponding only to major snowfall events. Given the model results and close correspondence between summer BC and VA, the likely source of BC from biomass burning is the conifer-rich boreal forest of eastern North America.

Northern Hemisphere industrial emissions of sulfur dioxide began in the mid-19th century with widespread burning of coal (*17*), and the ice-core record clearly reflects this (Fig. 2B). Before 1850, nss-S concentrations were generally low and primarily attributed to biogenic emissions (*14*), although the entire ice-core record is punctuated with very large, short-lived increases in nss-S resulting from fallout from well-known explosive volcanic eruptions. Long-term increases in nss-S began soon after 1850, accelerated sharply during the late 19th century, declined slowly from ~1910 to the late 1930s, and then increased strongly again through the early 1970s. In the early 1970s, implementation of the Clean Air Act lowered U.S. sulfur emissions (other countries also began regulating emissions), resulting in a peak in nss-S in the D4 ice-core record in ~1970 followed by a slow decline until ~1992 and a sharp drop almost to preindustrial levels by 2002.

Before 1850, when correlations between BC and VA were high, concentrations of nss-S were not correlated to either BC or VA, suggesting that forest fires were not a significant source of

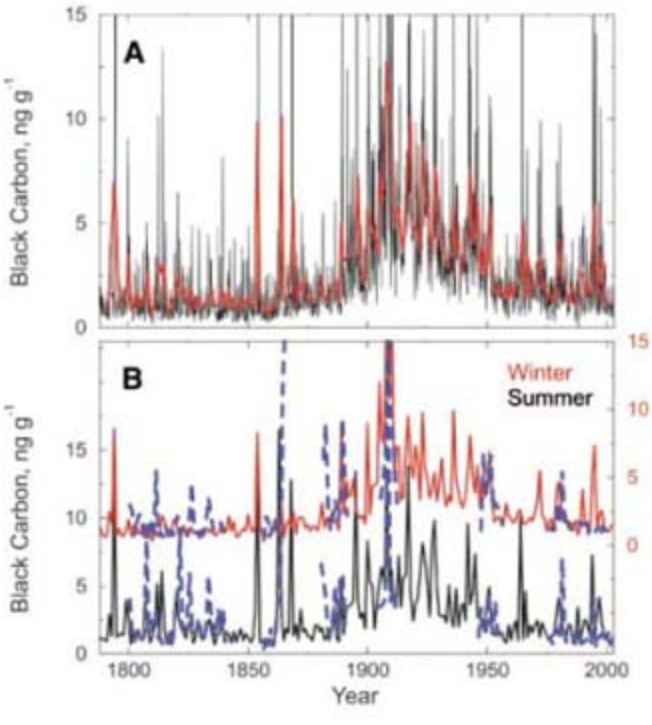


**Fig. 1.** (**A**) Monthly (black) and annual (red) BC concentrations from 1788 through 2002 measured in the Greenland D4 ice core. (**B**) Winter and summer BC concentrations show that long-term changes in BC were greater in winter (red) than in summer (black) during the late 19th and early 20th centuries. Winter and summer BC concentrations measured in the D5 ice core (*6*), located ~350 km south of the D4 site (blue dashed trace), indicate that observed BC changes were at least regional in extent. The maximum monthly BC value of 58.8 ng $g^{-1}$ occurred in summer 1854.

atmospheric sulfur. After 1850, highly correlated increases ($P < 0.0001$) in BC and nss-S concentrations indicate that industrial emissions became the primary source of BC. Correlations between annual, winter, and summer average BC and nss-S concentrations from 1850 to 1951 were 0.67, 0.74, and 0.59, respectively. Comparisons of BC and nss-S concentrations during winter, when forest fire–derived BC was at a minimum, indicate that for every ton of pollution nss-S deposited in winter precipitation from 1850 to 1951, an average of ~0.3 ton of BC was deposited concurrently (*6*). After 1951, the positive correlation between nss-S and BC concentration decreased dramatically. Despite large increases in industrial $SO_2$ emissions (*17*) and nss-S concentrations in the ice-core record, BC concentrations in the ice remained low. Some correlation between nss-S and BC concentrations, however, was still evident (annual: $r = 0.30$, $P < 0.02$), albeit substantially less significant than during the period of high BC concentrations.

Although not validated because of the paucity of historical 20th-century BC measurements before this study, estimates of industrial BC emissions have been made on the basis of records of fossil fuel combustion (*18*, *19*). Such estimates were determined using fuel- and technology-dependent emissions factors that relate BC emissions to fuel combusted. Technological changes through time, however, mean that emissions factors are highly uncertain. Of the estimates of 20th-century BC emissions reported by (*18*), our measurements of BC agree most closely with those from the United States. In particular, estimates of U.S. emissions show a rapid increase in the late 18th century, a leveling off and decline in the early 20th century, a sharp drop in the early 1950s, and a slow decline to the end of the century—very similar to the ice-core measurements. Some models suggest that a large fraction of Arctic pollutants originates in south Asia (*3*). From results of air-mass back-trajectory modeling (*6*), as well as comparisons of ice-core measurements of BC and lead (*20*) with estimated BC and lead atmospheric industrial emissions, we conclude that most of the industrial BC deposited in central Greenland precipitation probably came from North American emissions, at least during the period of high BC concentrations from 1850 to 1951. Since 1951, the positive BC trend in the core record attributed to industrial emissions (Fig. 2A) suggests that Asia may be the primary source today, which is consistent with other work (*3*).

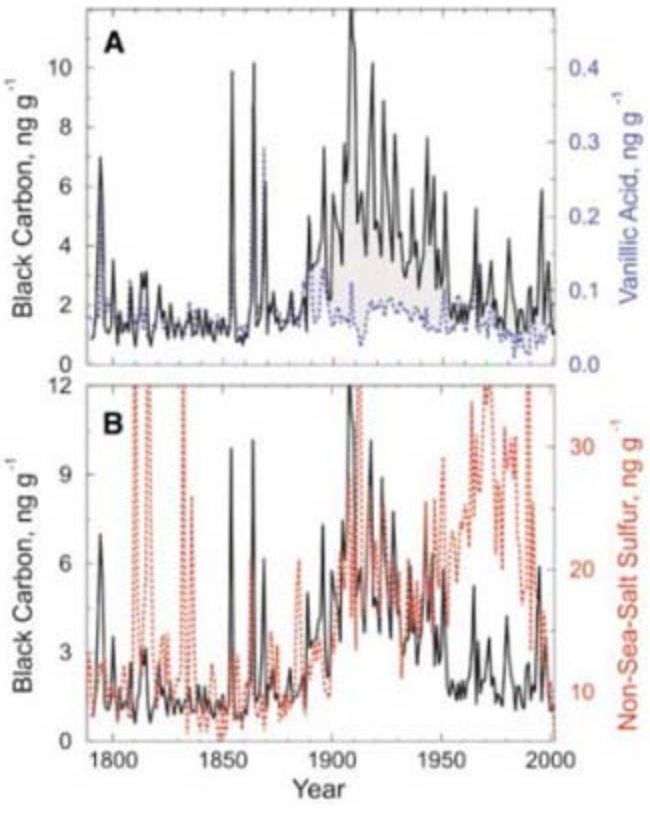


**Fig. 2.** (**A**) Annual average concentrations of BC and VA. The gray shaded region represents the portion of BC attributed to industrial emissions, not boreal forest fires. (**B**) Annual average concentrations of BC and nss-S. Large short-lived increases in nss-S result from explosive volcanism (such as Tambora, 1816; Krakatoa, 1883; and Katmai, 1912).

This monthly resolved record of BC in Arctic precipitation allows quantitative estimation of the impacts on climate forcing of BC in snow from both forest fires and fossil fuel burning during recent centuries. We used the Snow, Ice, and Aerosol Radiative (SNICAR) model (*11*), assuming an ice-grain effective radius of 100 μm and mass distributions measured in the ice core (a median particle mass of 1.82 fg and a geometric log-normal distribution width of 2.64) (*6*).

Because of large seasonal changes in incoming radiation at high latitudes and sometimes large seasonal changes in BC concentration in the ice-core record, radiative forcing from BC in snow in central Greenland is highly seasonal (*6*) and increased markedly during the late 19th and early 20th centuries as a result of industrial pollution. Monthly averaged surface forcing (i.e., BC-induced heating) during the peak early summer period (June and July) was ~0.28 W m$^{-2}$, with a median early summer forcing of ~0.20 W m$^{-2}$ before 1850, ~0.38 W m$^{-2}$ from 1850 to 1951, and ~0.22 W m$^{-2}$ after 1951. Forcing during the dark winter months was negligible. During the peak 5-year period from 1906 to 1910, forcing at the D4 ice-core site from BC in snow was 1.02 W m$^{-2}$, a fivefold increase from preindustrial conditions, with ~0.76 W m$^{-2}$ attributed to industrial pollution BC (Fig. 3A).

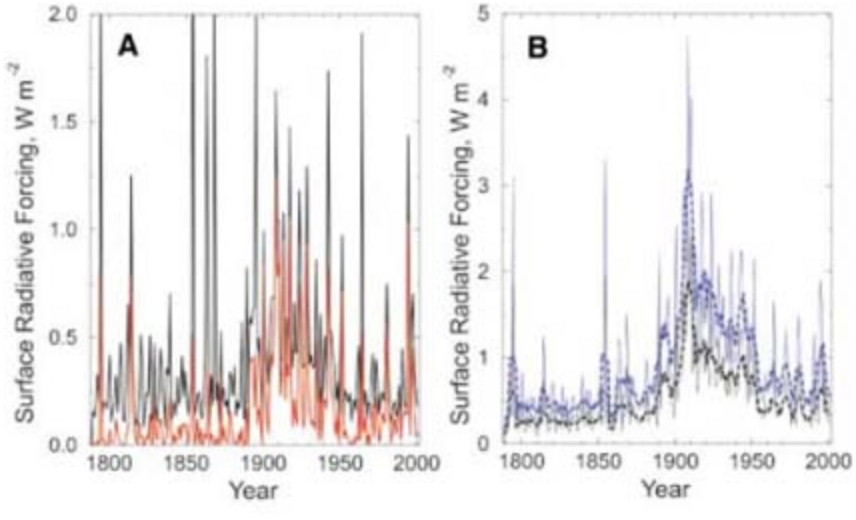


**Fig. 3.** (**A**) Surface radiative forcing from BC in snow during early summer (June and July) at the permanently snow-covered D4 ice core site. Forcing was modeled using SNICAR and monthly averaged total (black) and industrial (red) BC concentrations. (**B**) Estimated surface radiative forcing for a seasonal snow cover derived using mean winter BC concentration measured in the core and early summer solar forcing conditions (black). Average early summer surface forcing was extrapolated throughout the Arctic region (blue). The dashed lines show 5-year running means. Modeling of radiative forcing at the ice core site was for dry snow conditions because no surface melt occurs at D4. Although poorly known, redistribution of BC in a melting snow pack (*22*) may influence the impact of BC on forcing.

Although enhanced radiative forcing from BC in snow results in warming and possibly summer melting on the permanently snow-covered Greenland ice sheet, potential impacts on seasonal snow covers are larger because additional warming leads to earlier exposure of underlying low-albedo rock, soil, vegetation, and sea ice (*19*). Surface heating in seasonally snow-covered regions is primarily influenced by BC deposited during the snow accumulation period (December through May). Thus, early summer surface radiative forcing for a seasonally snow-covered site can be estimated using average BC concentration from December through July, measured in the ice core, and solar forcing conditions during the subsequent early summer

(Fig. 3B). In simulations with these conditions, the radiative impact of industrial BC emissions is substantially greater because winter concentrations increase more than summer concentrations as a result of industrialization.

To estimate the impact of changes in BC measured in ice cores throughout the Arctic region during the past 215 years, we used global model simulations of 1998 and 2001 radiative forcing from BC in snow to extrapolate model results at the ice-core site (*11*). The simulated average surface forcing of anthropogenic BC throughout the region from 60°N to 90°N was 1.7 times that at the ice-core site in Greenland. Assuming that this ratio has been approximately constant in time, we scaled monthly average surface forcing for the seasonal snow-cover simulation to approximate changes in average Arctic surface forcing during the same period (Fig. 3B). Although they are in agreement with these results in central Greenland, 1983–1984 spot measurements of BC indicated an Arctic/Greenland value of about 10 (*21*), suggesting that the impact from industrial BC emissions across the Arctic may have been significantly larger.

Pronounced increases in BC concentration in snow observed in the Greenland ice cores extrapolate to a marked impact on early summer climate forcing throughout the Arctic during and after industrialization, with changes largely attributed to winter industrial BC emissions (Fig. 3B). The median in estimated surface forcing in early summer throughout the Arctic was 0.42 W $m^{-2}$ before 1850, 1.13 W $m^{-2}$ during the period from 1850 to 1951, and 0.59 W $m^{-2}$ after 1951. During the 5-year period of maximum industrial BC emissions from 1906 to 1910, estimated surface forcing in the Arctic was 3.2 W $m^{-2}$, which is about eight times the typical early summer forcing before industrialization.

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### Supporting Online Material

www.sciencemag.org/cgi/content/full/1144856/DC1
Materials and Methods
Figs. S1 to S4
References


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# Saturn's Gravitational Field, Internal Rotation, and Interior Structure


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Saturn's internal rotation period is unknown, though it must be less than 10 hours, 39 minutes, and 22 seconds, as derived from magnetic field plus kilometric radiation data. By using the Cassini spacecraft's gravitational data, along with Pioneer and Voyager radio occultation and wind data, we obtain a rotation period of 10 hours, 32 minutes, and 35 ± 13 seconds. This more rapid spin implies slower equatorial wind speeds on Saturn than previously assumed, and the winds at higher latitudes flow both east and west, as on Jupiter. Our related Saturn interior model has a molecular-to-metallic hydrogen transition about halfway to the planet's center.


Because of its rapid rotation, Saturn is the most oblate planet in the solar system. The flattening of the planet can be seen even through a small telescope. However, the planet's internal rotation rate is not reflected in the measured periodicities in magnetic field data and Saturn kilometric radiation (SKR) data (*1*). Periodic signals coherent in period, amplitude, and phase over several months, including the Cassini rotation period of 10 hours, 47 min, 6 s (*2*), do not reflect the rotation of the deep interior but rather are based on a slippage of Saturn's magnetosphere relative to the interior, possibly due to a centrifugally driven instability in Saturn's plasma disk (*1*, *3*). For the purposes of obtaining a reference geoid and interior density distribution, both of which are dependent on Saturn's deep rotation rate, we analyze the available gravitational data (*4*) and radio occultation and wind data (*5*) with an approach free of any tight a priori constraints on Saturn's rotation period.


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The gravitational data reflect Saturn's interior density distribution and internal rotation rate, whereas the radio occultation and wind data reflect dynamical effects on the shape of a surface of constant pressure: the 100-mbar isosurface in Saturn's atmosphere. By finding a mean geoid (a static surface of equal gravitational potential energy) that both matches the gravitational data and minimizes the wind-induced dynamic heights of the 100-mbar isosurface with respect to the mean or reference geoid, we average out the dynamical effects on the atmosphere and obtain a static oblate Saturn model. We claim that this model, which minimizes the energy needed to drive the atmospheric winds, is a good approximation to the true physical state of Saturn below its atmosphere. The more rapid spin we find to be associated with the reference geoid affects atmospheric dynamics. The eastern wind speeds on the equator are reduced, corresponding to a reduction in the equatorial bulge from 122 to 10 km.

The history of the figures of celestial bodies in uniform rotation is a rich one and of considerable interest in itself [e.g., see chapter 1 in both (*6*) and (*7*)]. An important result from Newtonian mechanics, which is sufficient for the description of the shape of planetary bodies and stars, is that the external gravitational potential

function $V$ for a giant planet responding only to rotational forces can be expressed in a series of even Legendre polynomials $P_{2n}$ as in (*8*)

$$V = \frac{GM_S}{r}\left[1 - \sum_{n=1}^{\infty}\left(\frac{R_S}{r}\right)^{2n} J_{2n}P_{2n}(\sin\phi)\right] \quad (1)$$

where $M_S$ is the total mass of Saturn, $G$ is the gravitational constant, $R_S$ is an adopted reference radius for the gravitational field (60,330 km for Saturn, a radius that approximates its equatorial radius), $r$ is the radial distance, $J_{2n}$ are the numerical coefficients that describe the departure of the gravitational field from spherical symmetry, and $P_{2n}$ are the Legendre polynomials of degree $2n$. We obtained the equations of motion for a spacecraft, such as the Cassini spacecraft orbiting Saturn, by applying the vector gradient operator to a truncated series for $V$ to obtain the Cartesian vector equations $\ddot{\vec{r}} = \nabla V$, where $\vec{r}$ is the vector $(x, y, z)$ referenced to the planet's center of mass and dots represent the time derivative. The spherical coordinates are $r$ and the latitude $\phi$, which can be expressed in terms of equatorial Cartesian coordinates by $r = \sqrt{[(x^2 + y^2 + z^2)]}$ and $\sin\phi = z/r$. The equations actually integrated to obtain the position and velocity of the spacecraft are more complicated than this (*9*); in particular, they involve perturbations by other bodies (satellites, Sun, and planets), the precession of Saturn's pole in inertial space, and relativistic terms of order $c^{-2}$, where $c$ is the speed of light, but $\ddot{\vec{r}} = \nabla V$ represents the main orbital problem for spacecraft motion. The spacecraft mass is so small with respect to that of other bodies that it can be ignored. It has no measurable effect on the motions of other bodies in the system.

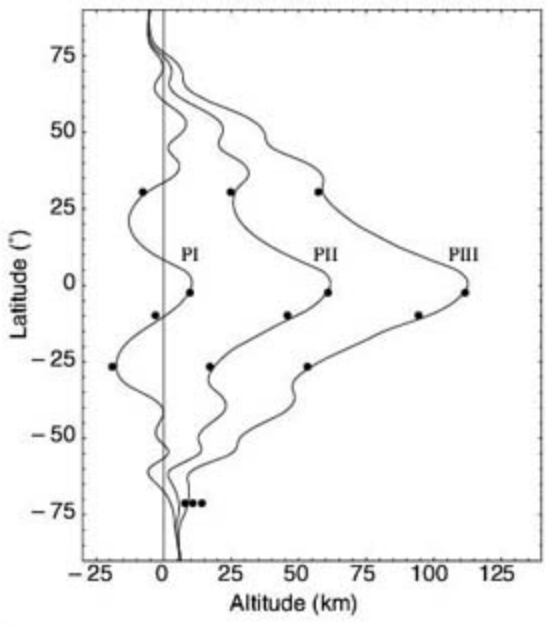


**Fig. 1.** Altitudes of the 100-mbar isobaric surface above a reference geoid with three different periods [10 hours, 32 min, 35 s (PI); 10 hours, 35 min, 35 s (PII); and 10 hours, 38 min, 35 s (PIII)], all shorter than the Voyager period of 10 hours, 39 min, 22.4 s (*24*) and hence consistent with recent findings on the variable rotation period of the inner region of Saturn's plasma disk (*1*). The circles represent radii obtained by radio occultation measurements with the Pioneer 11, Voyager 1, and Voyager 2 spacecraft (*5*). The polar radius is fixed at 54,438 km, which is consistent with the mean polar radius of 54,438 ± 10 km that best fits the five radio occultation radii (*5*). The solid curves represent a 100-mbar isosurface in geostrophic balance based on zonal-wind data obtained from the Voyager imaging system (*5*, *12*, *25*). The Cassini external gravitational field (*4*), the polar radius, and the rotation period are sufficient to define a reference geoid unperturbed by zonal winds: the vertical zero line. Over the 6-min period interval of the figure, the altitude of the equatorial bulge, in excess of the underlying reference geoid, is approximately linear in the rotation period.

The mass constant $GM_S$ and the gravitational coefficients $J_{2n}$ in the equation above are inferred from the Cassini radio Doppler data [see supporting online material (SOM) text]. The Doppler velocity is closely approximated by the velocity of the spacecraft projected on the line of sight between Earth and Saturn [the more exact relationship is given in (*9*) in terms of the actual data delivered by NASA's Deep Space Network (DSN)], and the velocity of the spacecraft is obtained by numerical integration of the equations of motion. The inversion of the DSN Doppler data to obtain the gravitational data is a standard nonlinear least-squares problem, where the Doppler data are expressed as a function of the spacecraft's initial state (position and velocity $\vec{r}$ and $\ddot{\vec{r}}$ at an arbitrary epoch) and the gravitational parameters ($GM_S$, $J_{2n}$). This constitutes the fitting model. Before the Cassini mission, the best determination of the zonal harmonic coefficients $J_{2n}$ was obtained by analyzing the radio Doppler data from a Pioneer 11 flyby in 1979, a Voyager 1 flyby in 1980, and a Voyager 2 flyby in 1981 (*10*), along with dynamical data on Saturn's rings (*11*).

We obtain the radio occultation data at the 100-mbar pressure level in Saturn's atmosphere from Pioneer and Voyager measurements (*5*). The recovered radii for the 100-mbar isosurface can be fit with a Cassini reference geoid with best-fit values of the reference period and equatorial radius (SOM text). Because the 100-mbar isosurface agrees with the occultation radii, except for one outlier near 71.2°S latitude, we ignore the occultation radii in our calculations. However, they are useful as a check on the calculations.

The heights of the 100-mbar isosurface are plotted before any fitting in Fig. 1 for three periods of rotation. Because Gurnett *et al.* (*1*) conclude that any rotation period of the body of Saturn, unperturbed by winds, must be less than the Voyager period, these three periods are representative of an interval of upper and lower bounds on the rotation period. One of the most puzzling features of the plot is why the polar radius at the north and south poles should differ by ~10 km. It is hard to understand how a planet as massive as Saturn could maintain an offset between its center of figure and center of mass of fractional magnitude ~ $10^{-4}$.

We adopt the curve labeled PI in Fig. 1 as the best representation of Saturn's 100-mbar isosurface, because it minimizes the height excursions of this surface with respect to the surface of the mean geoid (fig. S1). The period of rotation is 10 hours, 32 min, 35 ± 13 s. We suggest that this rotation period, which is consistent with the upper bound from all previous data, is the period of rotation of Saturn's deep interior. The reference geoid is symmetric about the equator and corresponds to a uniform period; it yields minimum [in a root mean square (rms) sense over all latitudes] dynamic heights of the 100-mbar isosurface, and it corresponds to an external gravitational field that agrees with the field determined by the Cassini radio Doppler data. In Table 1, we compare the "best-fit" reference geoid for both the older gravitational field detected by Voyager (*10*) and the gravitational field more recently detected by Cassini (*4*). The statistical errors in the first five fitted parameters of Table 1 are considerably smaller for the Cassini reference geoid, showing the advantage of including the Cassini data in the analysis. The Voyager results could have been obtained over 20 years ago. Indeed, it

**Table 1.** Best-fit parameters for both the a priori Voyager and Cassini gravitational data. The gravitational coefficients $J_2$, $J_4$, and $J_6$ are constrained by their a priori mean values and associated covariance matrix from respective Voyager (*10*) and Cassini (*4*) Doppler fits. This effectively produces a reference geoid that fits the gravitational data and minimizes the rms dynamic heights of the Voyager 100-mbar isosurface (*5*). The period $P$ and equatorial radius $a$ are statistically consistent for Voyager and Cassini. Further, there is no significant improvement in the Cassini gravity field. However, the Voyager gravity field is improved by minimizing the heights of the 100-mbar isosurface. In particular, the coefficient $J_6$ is brought more in line with the Cassini fit. The gravitational coefficients $J_2$ through $J_{10}$ are given in units of $10^{-6}$. The a priori constraints on $J_8$ and $J_{10}$ are adopted as reasonable values that condition the fits. h, hours; m, minutes.

| Parameter | Voyager a priori | Voyager fit | Cassini a priori | Cassini fit |
|---|---|---|---|---|
| $P$ | None | 10 h, 32 m, 55 ± 30 s | None | 10 h, 32 m, 35 ± 13 s |
| $a$ (km) | None | 60352.0 ± 6.8 | None | 60356.2 ± 2.6 |
| $J_2$ | 16298 ± 10 | 16298 ± 10 | 16290.71 ± 0.27 | 16290.73 ± 0.26 |
| $J_4$ | −915 ± 40 | −906 ± 37 | −935.8 ± 2.8 | −935.5 ± 2.5 |
| $J_6$ | 103 ± 50 | 79 ± 23 | 84.1 ± 9.6 | 85.3 ± 8.5 |
| $J_8$ | −10 ± 3 | −10 ± 3 | −10 ± 3 | −10 ± 3 |
| $J_{10}$ | 2 ± 1 | 2 ± 1 | 2 ± 1 | 2 ± 1 |

**Table 2.** Geodetic and interior parameters for four rotation periods that span the interval of possible Saturn rotation periods. The rotation is expressed in terms of the angular velocity $\omega = 2\pi/P$ and either the equatorial radius $a$ by the smallness parameter $q = \omega^2 a^3/GM_S$ or the mean radius $R$ by $m = \omega^2 R^3/GM_S$. The mean density $\rho_0$ is the density of a sphere with volume equal to the volume of Saturn's reference geoid $(4/3)\pi R^3$. The pressure $p_0$ is a characteristic internal pressure given by $p_0 = GM_S\rho_0/R$. The central density $\rho_c$ and the central pressure $p_c$ are calculated by integrating the equations of hydrostatic equilibrium and mass continuity with the adopted polynomial density distribution. The column in the table for a rotation period of 10 hours, 32 min, 35 s represents our recommended interior model for Saturn.

| Parameter | 10 h, 32 m, 35 s | 10 h, 35 m, 35 s | 10 h, 38 m, 35 s | 10 h, 41 m, 35 s |
|---|---|---|---|---|
| $a$ (km) | 60357.3 | 60305.7 | 60254.8 | 60204.9 |
| $R$ (km) | 58256.3 | 58224.3 | 58192.8 | 58161.9 |
| $q$ | 0.158904 | 0.157002 | 0.155136 | 0.153307 |
| $m$ | 0.142879 | 0.141300 | 0.139748 | 0.138224 |
| $\rho_0$ (kg m$^{-3}$) | 686.244 | 687.378 | 688.494 | 689.591 |
| $p_0$ (Mbar) | 4.46819 | 4.47804 | 4.48774 | 4.49728 |
| $J_2$ ($10^{-6}$) | 16276.0 | 16303.8 | 16331.4 | 16358.5 |
| $J_4$ ($10^{-6}$) | −934.1 | −937.3 | −940.5 | −943.6 |
| $J_6$ ($10^{-6}$) | 83.9 | 84.3 | 84.7 | 85.2 |
| $\rho_c$ (kg m$^{-3}$) | 3080.07 | 3022.82 | 2965.97 | 2909.74 |
| $p_c$ (Mbar) | 9.11744 | 8.88905 | 8.66533 | 8.44742 |

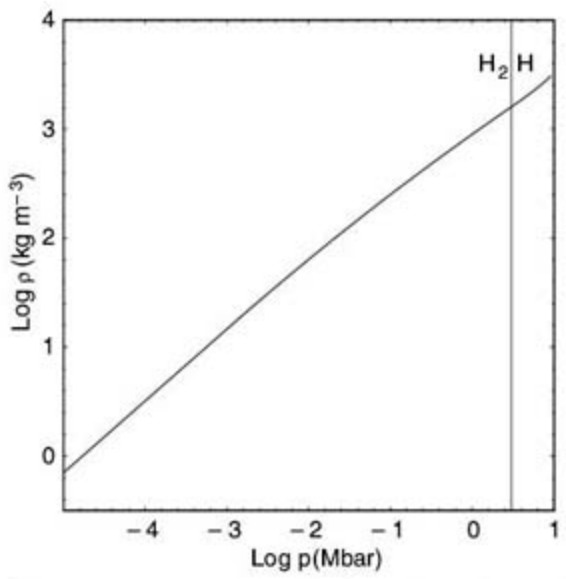


**Fig. 2.** A pressure $p$ and density $\rho$ EOS inferred from a sixth-degree polynomial interior model that fits the Cassini gravitational data (*4*) and rotates at a rate that minimizes wind perturbations (*5*), not at the slower rate previously assumed for Saturn (*1*). The vertical line is at a pressure of 3 Mbar, representative of the region where the transition from molecular to metallic liquid hydrogen occurs (*16*).

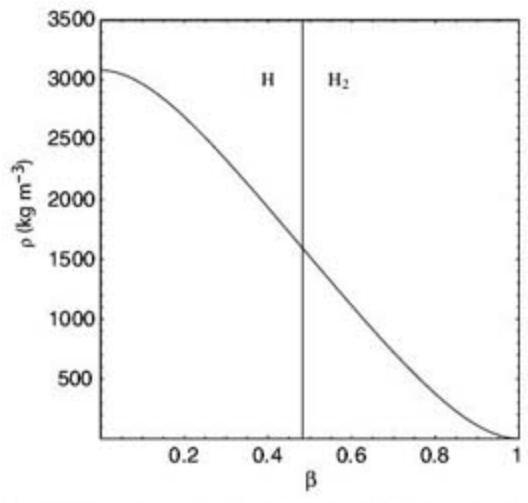


**Fig. 3.** The density $\rho$ in Fig. 2 plotted against $\beta$.

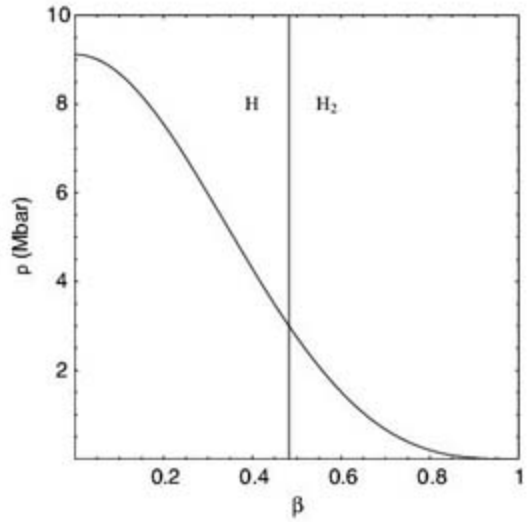


**Fig. 4.** The pressure $p$ in Fig. 2 plotted against $\beta$.

was pointed out at the time of the Voyager wind analysis (*12*) that a more rapid Saturnian rotation rate would result in lower wind velocities with respect to the solid-body rotation, but there was no reason then to question the rotation period inferred from SKR and magnetic field data. Now we know that the solid-body rotation is unknown (*1*) but that it most likely falls within a period interval of ~6 min. For this reason, we calculate interior models for the four periods and the four corresponding reference geoids of Table 2.

The idea behind the interior calculations for a reference geoid is to integrate the equations of hydrostatic equilibrium with the boundary conditions that pressure and density are zero at the surface (SOM text). We represent the fractional density by a sixth-degree polynomial in fractional mean radius $\beta$. The first-degree term is set to zero so that the derivative of the density goes to zero at the center ($\beta = 0$). This simple model does not directly account for the molecular-to-metallic phase change of hydrogen in the interior or the variation with depth in the concentration of elements like helium that are thought to occur (*13*). It is consistent with the Zharkov-Trubitsyn method of gravity sounding (*14*, *15*). The sixth-degree polynomial is continuous, unlike a density distribution with discontinuities at phase transitions or with a core of different composition than that of the envelope. The polynomial smooths out any real discontinuities in the density distribution. In the sense that it fits all the currently available data on the shape and gravitational field of Saturn, the polynomial can serve as a useful approximation to more detailed models that include the physics of the equation of state (EOS). We match the sixth-degree polynomial to the measured gravitational coefficients $J_2$, $J_4$, and $J_6$ by the third-order theory of level surfaces (*14*).

The results are shown in Table 2 for four rotation periods, from a lower bound of 10 hours, 32 min, 35 s (the period corresponding to PI in Fig. 1), which is consistent with our best-fit reference geoid, to an upper bound of 10 hours, 41 min, 35 s, which is somewhat less than the previously adopted rotation period for Saturn. We rule out any periods shorter than PI because that would result in the interior of Saturn rotating more rapidly than the surface winds suggest. Density and pressure for the reference geoid PI are plotted parametrically in Fig. 2 and are shown separately versus depth in Figs. 3 and 4, respectively. A pressure of 3 Mbar occurs at about $\beta$ = 0.48, which is consistent with a transition from molecular to metallic hydrogen at this depth. The parametric plot of Fig. 2 is in good agreement with a physical EOS derived from experiments with deuterium under high pressures (*16*).

We have shown that Saturn's mass, radius, and gravitational coefficients $J_2$, $J_4$, and $J_6$ can be fit by a simple model of the planet's interior, based on a sixth-degree polynomial (SOM text). The polynomial probably underestimates the mass of a core of a different chemical composition from that of the envelope, especially with a likely density jump at the core-envelope boundary. Current models of Saturn's interior have cores with masses between about 10 and 20 Earth masses (*13*, *16*–*20*). In some of these previous models (*13*, *20*), even the larger core estimates are lower bounds, because core mass trades off against helium and heavy element separation and concentration at depth in the models. Recent models of Saturn's interior divide the planet into multiple regions, consisting of at least a molecular hydrogen-helium outer envelope surrounding a metallic hydrogen layer and a rock-ice core at the center. These models are characterized by many parameters, and they are beset by uncertainties in the EOS of hydrogen and the phase diagram of hydrogen-helium mixtures (*21*). The simple polynomial model of this paper suffices to fit the gravitational coefficients. The ability of a simple polynomial model to fit the gravitational data diminishes the

necessity for inhomogeneity in the interior composition of Saturn, although phase separation of helium seems to be necessary to explain the planet's heat flux and evolution (*20*). Core accretion theory (*22*, *23*) of the planet's formation requires a critical core mass of about 10 Earth masses for rapid accretion of its gaseous hydrogen-helium envelope.

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### Supporting Online Material

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SOM Text
Fig. S1
References


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# Asymmetry in the Structure of the ABC Transporter–Binding Protein Complex BtuCD-BtuF


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**BtuCD is an adenosine triphosphate–binding cassette (ABC) transporter that translocates vitamin $B_{12}$ from the periplasmic binding protein BtuF into the cytoplasm of *Escherichia coli*. The 2.6 angstrom crystal structure of a complex BtuCD-F reveals substantial conformational changes as compared with the previously reported structures of BtuCD and BtuF. The lobes of BtuF are spread apart, and $B_{12}$ is displaced from the binding pocket. The transmembrane BtuC subunits reveal two distinct conformations, and the translocation pathway is closed to both sides of the membrane. Electron paramagnetic resonance spectra of spin-labeled cysteine mutants reconstituted in proteoliposomes are consistent with the conformation of BtuCD-F that was observed in the crystal structure. A comparison with BtuCD and the homologous HI1470/71 protein suggests that the structure of BtuCD-F may reflect a posttranslocation intermediate.**


Adenosine triphosphate (ATP)–binding cassette (ABC) transporters are integral membrane proteins that use the energy gained from hydrolyzing ATP to drive the transport of diverse substrates across cellular membranes (*1*). In bacteria, binding protein–dependent ABC importers facilitate the uptake of essential nutrients from the environment (*2*). One such protein is the *Escherichia coli* vitamin $B_{12}$ transporter BtuCD (*3*, *4*) that is related in sequence and mechanism to iron-siderophore transporters associated with the virulence of certain pathogenic bacteria (*5*, *6*). Like other ABC transporters, BtuCD consists of two transmembrane domains (TMDs) (i.e., BtuC subunits) that form a pathway for the substrate and two cytoplasmic nucleotide-binding domains (NBDs) (BtuD subunits) that bind and hydrolyze ATP. The fold of the NBDs and their arrangement in ABC transporters are conserved, whereas the architectures of the TMDs are not (*2*). For example, BtuCD has 20 transmembrane (TM) helices, distinct from the 12 TM helices of the multidrug exporter Sav1866 (*7*) or the molybdate/tungstate importer ModBC (*8*). The cognate periplasmic binding protein of BtuCD is BtuF, which captures $B_{12}$ and feeds it to the external side of the transporter (*9*).

A detailed understanding of transport phenomena requires direct visualization of the transporters in different conformations and at high resolution. At the present time, no ABC transporter has been visualized in more than one state, illustrating the challenges involved. Here we present the structure of a BtuCD-F complex (stoichiometry $BtuC_2D_2F$), which has captured a conformation that may reflect a posttranslocation intermediate. We compared this structure with those previously determined of BtuCD (*10*) and BtuF (*11*, *12*) and with that of the homologous metal-chelate transporter HI1470/71 (*13*). We found substantial structural changes that may be relevant for formulating a transport mechanism.

To generate BtuCD-F, we exploited an earlier finding (*11*, *14*) and added $B_{12}$-bound BtuF to detergent-lyzed *E. coli* cells overexpressing BtuCD (*15*). From this mixture, we purified a BtuCD-F complex that is colorless and therefore devoid of bound $B_{12}$. We used a mutant of BtuCD with all surface-exposed cysteines replaced by serines ("cys-less"), which offered the advantage that it was also suitable for spin labeling and electron paramagnetic resonance (EPR) spectroscopy. Cys-less BtuCD has unchanged adenosine triphosphatase (ATPase) activity as compared to native BtuCD and also shows a characteristic, nearly twofold stimulation of ATP hydrolysis rates upon the addition of $B_{12}$-bound BtuF (ATP hydrolysis rates of $492 \pm 17$ nmol $mg^{-1}$ $min^{-1}$ for BtuCD and $784 \pm 8$ nmol $mg^{-1}$ $min^{-1}$ for BtuCD-F at room temperature).

The crystal structure of the BtuCD-F complex (Fig. 1) revealed that BtuF is bound to the periplasmic face of BtuCD. Although the diffraction data extended to 2.6 Å (table S1), high-quality electron density was visible for only the BtuC and BtuD subunits, whereas in the region of BtuF, the electron density was not as good (fig. S1A). This probably reflects the flexibility of BtuF when bound to the transporter or the absence of lattice contacts involving BtuF. The experimental electron density nevertheless allowed for unambiguous tracing of BtuF, using the previously determined high-resolution structure as a template.

In the structure of BtuCD-F, the binding protein is devoid of substrate, which is remarkable given the high affinity (~15 nM) of isolated BtuF for $B_{12}$ (*9*). The loss of $B_{12}$ from the binding pocket correlates with a substantial opening or spreading of the two lobes (N lobe and C lobe) of BtuF and with the insertion of periplasmic BtuC loops into the $B_{12}$ binding pocket. When the N lobe of the structure of BtuF in isolation is superimposed onto that of the complex, the change in the C lobe can be described as a pivoting by ~8°


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around a hinge approximately located at the C-terminal end of the "backbone helix" of BtuF (Fig. 2). As a consequence, the regions of the C lobe in contact with BtuCD are shifted outward by some 4 Å, away from the $B_{12}$ binding site. Lobe opening has previously been suspected to be important for substrate delivery of other binding protein–dependent ABC importers (*16*), but no sizeable lobe opening was observed in the crystal structure of apo-BtuF (*12*), suggesting that binding to BtuCD is critical for this event.

The contact interface between BtuF and $BtuC_2$ involves the two nonidentical lobes of BtuF (Fig. 1B). Each lobe contacts primarily one BtuC subunit, thus inducing slight asymmetry in the periplasmic loops of the two BtuC subunits. The interface involves various BtuC loops, including parts of helix 5a (Fig. 1C). There are several charged residues participating in the interface, which is consistent with observations seen in other ABC importers (*8*, *17*, *18*). In particular, it was predicted that arginine residues from BtuC, conserved in metal-chelate type ABC importers, may interact with conserved glutamate residues on the surface of BtuF (*11*). Our BtuCD-F structure confirms this prediction and reveals salt bridges between $Arg^{56}$ residues from both BtuC subunits and the glutamate residues $Glu^{74}$ and $Glu^{202}$ from BtuF. These salt bridges appear to be important for proper interaction in vivo, because the deletion of the analogous glutamate residues in the ferrichrome binding protein FhuD abolished transport (*18*). We also found that mutating $Glu^{74}$ of *E. coli* BtuF into an alanine residue prevents the efficient formation of the BtuCD-F complex in vitro. The periplasmic loops between TM5 and helix 5a from both BtuC subunits reach into the $B_{12}$ binding site, partially occupying the space of previously bound $B_{12}$. Combined with the spreading of the lobes of BtuF, the insertion of periplasmic BtuC loops is probably responsible for triggering $B_{12}$ displacement from the binding pocket.

The BtuD subunits (NBDs) reveal a nucleotidefree "open" conformation with a gap between the P loops (phosphate-binding loops) and the LSGGQ (Leu-Ser-Gly-Gly-Gln) motifs of opposing NBDs. It has been noted earlier (*8*) that there are substantial structural differences between the nucleotidefree states of the full transporters ModBC, HI1470/71, and BtuCD and the NBD dimer from the maltose transporter $MalK_2$ (*19*). This is in contrast to the highly similar conformations of the ATP-bound states, as revealed by the structures of the multidrug transporter Sav1866 and various ATP-bound NBD dimers (*7*, *19*–*22*). There are no substantial structural changes of the BtuD subunits in BtuCD-F when compared to those observed in BtuCD, suggesting that for substrate-induced ATPase stimulation, only changes in the flexibilities of the NBDs (but no distinct structural changes) may be necessary.

The BtuC subunits are thought to provide a central translocation pathway for $B_{12}$. Whereas twofold rotational symmetry related these subunits in the original structure of BtuCD (*10*), BtuCD-F reveals striking asymmetry that is primarily evident in the helices TM3, TM4, TM5, and 5a but to a smaller extent also in other helices. The observed asymmetry is relatively moderate at the interface with BtuF (Fig. 1, B and C) but is very substantial at the cytoplasmic side of the membrane (Fig. 1D). Helices TM3 to 5a form a subset of TM helices whose orientations appear to control to which side of the membrane the translocation pathway is exposed. In the HI1470/71 structure, this subset was found to be distinct in conformation as compared with BtuCD, causing HI1471 to adopt an inward-facing conforma-

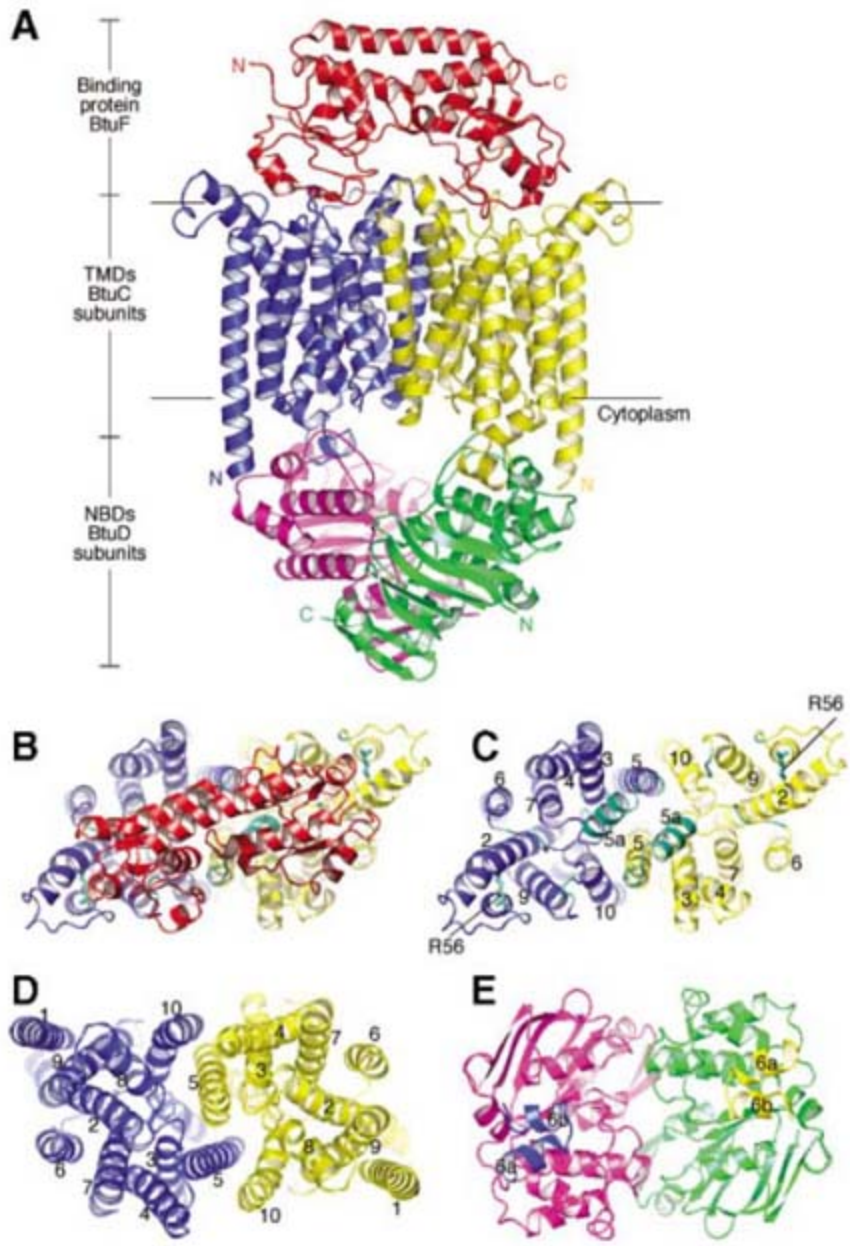


**Fig. 1.** Structure of the BtuCD-F complex in ribbon representation. (**A**) Front view, illustrating the arrangement of the five protein subunits. The horizontal lines indicate the approximate boundaries of the membrane. N and C denote the amino and carboxyl termini, respectively. (**B**) View from the periplasmic side. Regions of the BtuC subunits in contact with BtuF are teal. (**C**) Similar to (B) but for clarity, BtuF is not shown. The TM helices are numbered, and the regions in contact with BtuF are teal. The arginine residue conserved in metal-chelate–type ABC importers (R56) is shown as sticks and indicated. (**D**) BtuC subunits viewed from the cytoplasm; helices are numbered. The pronounced asymmetry of TM5 and, to a lesser degree, TM3 and TM4 is shown. (**E**) BtuD subunits and the BtuC helices 6a and 6b (previously labeled L helices) viewed from the membrane. Helix 6b is the coupling helix, a feature also present in other ABC-transporter structures.

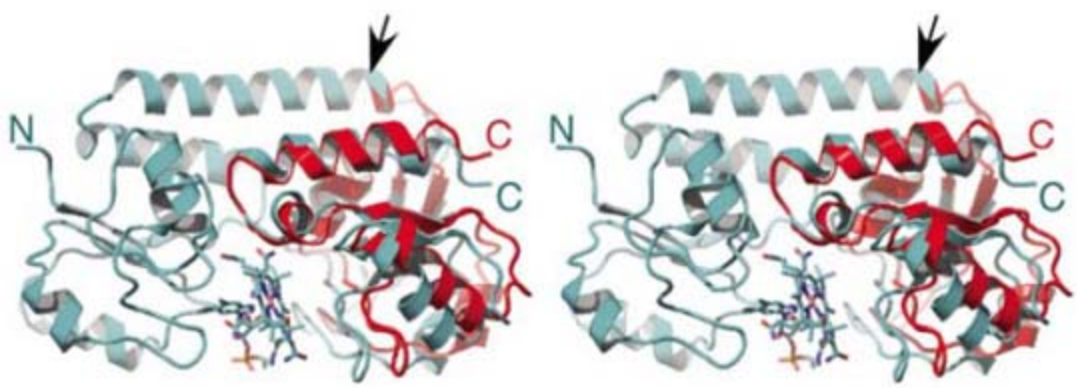


**Fig. 2.** Conformational changes in BtuF. A stereo figure of the structure of isolated, $B_{12}$-bound BtuF (*11*, *12*) is shown in light blue, and that of BtuF, devoid of $B_{12}$ and in complex with BtuCD, is shown in red. The view is from the side, and the superposition is based on the N lobe of BtuF (left lobe in the present view). As a result, only the C lobe reveals substantial changes, and for clarity, the N lobe of BtuCD-bound BtuF is not shown. The arrow denotes the C-terminal end of the backbone helix (top of the figure) of BtuF.

tion, whereas BtuCD was outward-facing. In BtuCD-F, helices TM3 to 5a of one BtuC subunit (yellow in Figs. 1 and 3; interacting mostly with the C lobe of BtuF) are similar in conformation to BtuCD, whereas the same helices of the other BtuC subunit (blue in Figs. 1 and 3; interacting mostly with the N lobe of BtuF) are similar to HI1471 (Fig. 3). This is reflected in the crossing angles of TM5 in the three crystal structures (table S2). As a consequence of the asymmetric conformations of helices TM3 to 5a, the central cavity in BtuCD-F is accessible to neither side of the membrane and appears too small to harbor a $B_{12}$ molecule.

A structure-based alignment of BtuC and HI1471 (fig. S3) indicates conserved hydrophobic residues in TM5 and helix 5a. These include $Leu^{146}$ and $Leu^{147}$ at the cytoplasmic side of TM5 and $Leu^{172}$ and $Met^{176}$ in helix 5a. In BtuCD-F, these residues shield the central cavity from the cytoplasm and the periplasm. Analogous hydrophobic residues are also present in the amino acid sequences of other metal-chelate ABC importers such as the *E. coli* ferrichrome importer FhuB, suggesting a common role in gating.

Because the asymmetrically occluded conformation of BtuCD-F was notable and unexpected, we sought to confirm its relevance in lipidic membranes. Hence, we introduced cysteine side chains at strategically placed positions in BtuC, in the loops preceding and following the key transmembrane helix TM5 (residues $Ser^{141}$ and $Thr^{168}$, respectively). Because of the stoichiometry, each mutation introduced two cysteines in the assembled transporter. We modified the engineered cysteines with spin labels and recorded continuous-wave (CW) EPR spectra of BtuCD and BtuCD-F after reconstitution in proteoliposomes, which mimic the native environment of membrane proteins. CW EPR spectra reflect the local dynamics of spin labels, which is influenced by the environment of the protein (*23*). At the same time, the spectra can reveal spin-spin coupling if the distance between two spin labels becomes short enough (<20 Å) (*24*). Our spectra (Fig. 4) show considerable differences between BtuCD and BtuCD-F. At the periplasmic side of the membrane, the spin labels at position 168 reveal substantial mobility in BtuCD, with two clearly defined dynamic components. The addition of $B_{12}$-bound BtuF appears to restrict the overall dynamics, and coupling between spin labels becomes evident in the spectrum, indicating a shortened distance between the labels. The spectra are consistent with the structures of BtuCD and BtuCD-F. In the latter, the distance between Cα positions of the residues 168 from the BtuC subunits decreased to ~14 Å from >25 Å in BtuCD. In addition, the external loops between TM5 and helix 5a extensively interact with BtuF, which probably accounts for the decreased mobility of the labels in BtuCD-F.

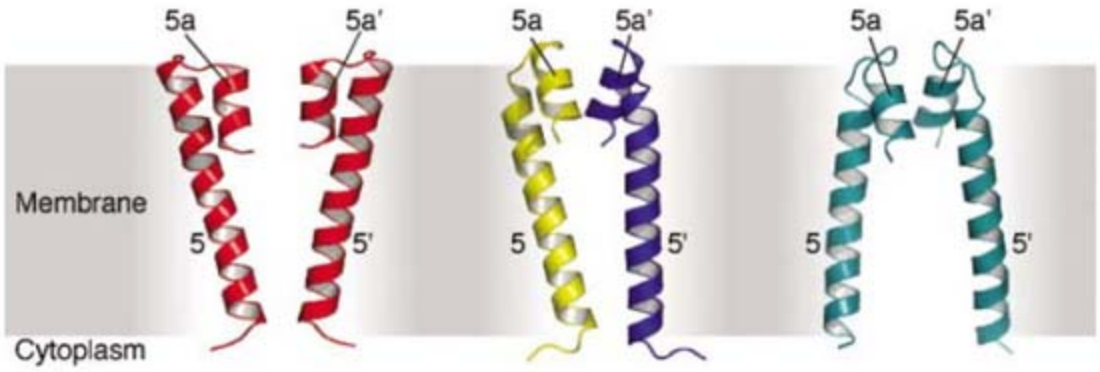


**Fig. 3.** Comparison of the TMD conformations of BtuCD (red), BtuCD-F (yellow and blue), and HI1470/71 (teal). For clarity, only helices TM5 and 5a from both TMDs are shown after the superposition of the NBDs and all TM helices except TM3, TM4, TM5, and 5a. For a stereo figure of the superimposed structures, see fig. S2.

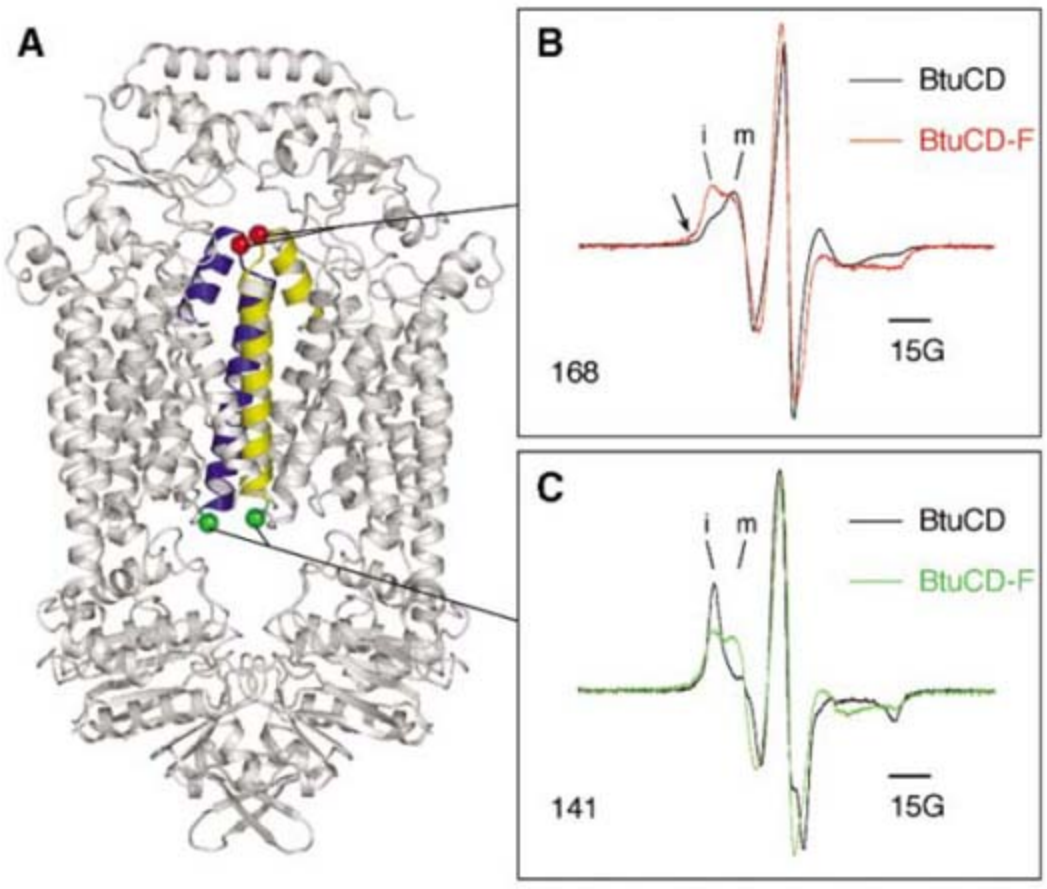


**Fig. 4.** EPR studies of BtuCD and BtuCD-F. (**A**) Strategically placed reporter labels 141 and 168 in the BtuC subunits are indicated by green and red spheres, respectively. They are located in the cytoplasmic loop preceding TM5 (position 141) and in the periplasmic loop between TM5 and helix 5a (position 168). (**B**) Normalized CW EPR spectra of BtuCD and BtuCD-F (black and red, respectively) after spin labeling at position 168 and reconstitution in proteoliposomes. Mobile (m) and immobile (i) components of the spectra are shown, and the region of the spectrum revealing spin-spin coupling is indicated with an arrow. The scale bar represents 15 gauss. (**C**) Similar to (B) but with spin labels at position 141. The spectra of BtuCD and BtuCD-F are in black and green, respectively.

At the cytoplasmic side of the membrane (in the loop between TM4 and TM5), the differences between the spectra are even more dramatic. In BtuCD, the labels at position 141 are highly immobile (almost at the rigid limit), consistent with their location at the center of the transporter in an outward-facing conformation. The addition of $B_{12}$-bound BtuF and the formation of BtuCD-F lead to two distinct components in the spectrum, one indicating an immobile label, the other a mobile label. Although we cannot rule out the possibility that the two components are the result of a dynamic exchange of labels between two environments, the BtuCD-F structure offers a simpler interpretation: The asymmetry between the BtuC subunits probably causes the two labels to face distinctly different environments (Fig. 1D). Whereas residue 141 of one BtuC subunit (yellow in Fig. 1D) is located at the center of the complex, where the flexibility of the spin label is probably restricted, that of the other BtuC subunit (blue in Fig. 1D) is at the periphery, where the label may experience a much higher conformational flexibility. This interpretation predicts equal contributions of the mobile and immobile components in the EPR spectra, which agrees with a quantitative analysis of the spectra (fig. S4). The EPR spectra are thus consistent with the conformations of the TM5 helices that were observed in the crystal structures of BtuCD and BtuCD-F (Fig. 3), and we conclude that both

structures probably reflect conformations that are relevant in native membranes.

On the basis of biochemical data and the structures of full ABC transporters determined in recent years, a conserved coupling mechanism for ABC transporters has recently been proposed that suggests that binding of ATP to the NBDs promotes an outward-facing conformation of the TMDs, whereas a release of the hydrolysis products promotes an inward-facing conformation (*8*, *25*). ABC importers would thus acquire substrates from their binding proteins in the ATP-bound state and release the substrates to the cytoplasm upon dissociation of the ATP hydrolysis products (*2*). This basic two-state scenario is in agreement with the structures of Sav1866, HI1470/71, and ModBC, which all visualize such states, whereas those of BtuCD and BtuCD-F reveal intermediate conformations. Although there may be differences in the detailed transport mechanism of BtuCD when compared with that of the maltose transporter MalFGK or the molybdate/tungstate transporter ModBC, BtuCD may nevertheless largely follow the common coupling mechanism of ABC transporters.

The BtuCD-F complex is stable in the absence of ATP, which is different from MalFGK or ModBC, where ATP and vanadate are required to generate stable complexes with the binding proteins (*8*, *26*). Even though the interaction of BtuCD with BtuF is sufficient to release $B_{12}$ from the high-affinity binding site, the transport of $B_{12}$ across the membrane requires ATP both in vivo and in vitro. During a productive transport cycle, $B_{12}$ is probably fed into an outward-facing conformation such as that observed in the structure of BtuCD and later released into the cytoplasm from an inward-facing conformation similar to that revealed by HI1470/71. The BtuCD-F structure presented here is a conformation that is, with respect to its TMDs, an intermediate between those of BtuCD and HI1470/71. This suggests that during the conversion from the inward- to the outward-facing conformation, the BtuC subunits may not alter their conformations simultaneously.

Unlike BtuCD, many other ABC transporters have pairs of TMDs with distinct amino acid sequences, which may have mechanistic consequences. The structure of BtuCD-F provides an opportunity to study conformational asymmetry at high resolution, which could prove useful for the mechanistic understanding of intrinsically asymmetric ABC transporters.

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### Supporting Online Material

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# LeuT-Desipramine Structure Reveals How Antidepressants Block Neurotransmitter Reuptake


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Tricyclic antidepressants exert their pharmacological effect—inhibiting the reuptake of serotonin, norepinephrine, and dopamine—by directly blocking neurotransmitter transporters (SERT, NET, and DAT, respectively) in the presynaptic membrane. The drug-binding site and the mechanism of this inhibition are poorly understood. We determined the crystal structure at 2.9 angstroms of the bacterial leucine transporter (LeuT), a homolog of SERT, NET, and DAT, in complex with leucine and the antidepressant desipramine. Desipramine binds at the inner end of the extracellular cavity of the transporter and is held in place by a hairpin loop and by a salt bridge. This binding site is separated from the leucine-binding site by the extracellular gate of the transporter. By directly locking the gate, desipramine prevents conformational changes and blocks substrate transport. Mutagenesis experiments on human SERT and DAT indicate that both the desipramine-binding site and its inhibition mechanism are probably conserved in the human neurotransmitter transporters.


Sodium- and chlorine ion–dependent neurotransmitter transporters for serotonin (SERT), norepinephrine (NET), and dopamine (DAT) in the presynaptic plasma membrane terminate neuronal signal transmission in the central nervous system through a reuptake mechanism (*1*–*6*). These systems have been shown to modulate mood, emotion, sleep, and appetite (*7*). Depression, arguably the most prevalent psychiatric disorder, is directly associated with perturbation of serotonergic neurotransmission (*8*, *9*), and drugs blocking serotonin reuptake have been used successfully for its treatment. One class of these drugs, tricyclic antidepressants (TCAs) such as desipramine and imipramine, binds to serotonin and norepinephrine transporters with affinities of nanomolar to tens of nanomolar concentrations and blocks transport activity (*10*). The response rate of patients to TCAs is typically 60 to 70% (*11*). More recently, highly selective serotonin-reuptake inhibitors (SSRIs) such as fluoxetine (Prozac) have also been developed and are increasingly


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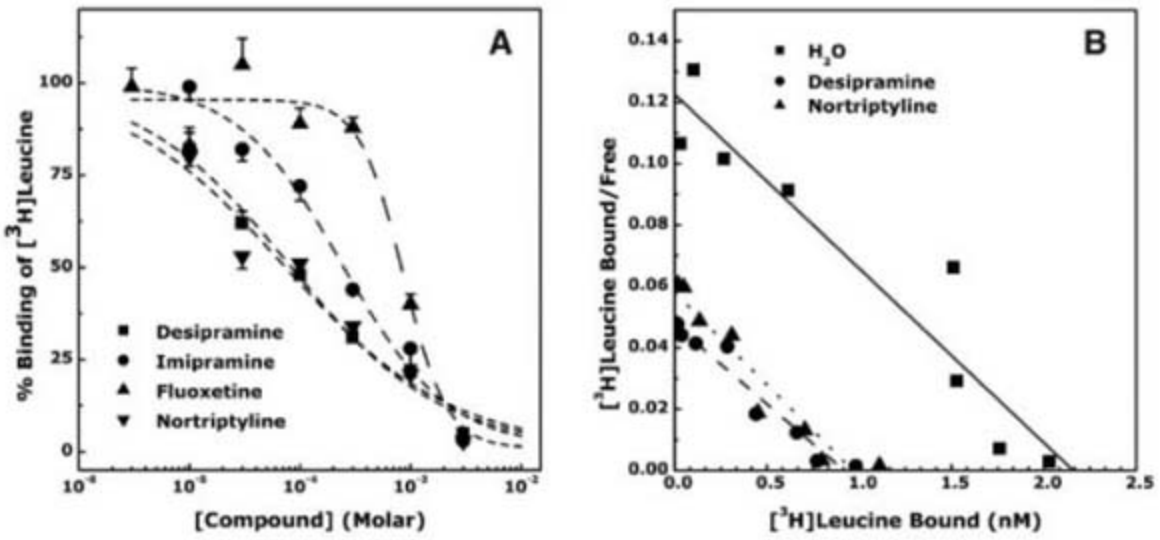


**Fig. 1.** Binding of various antidepressants and other compounds to LeuT. (**A**) Affinity of desipramine, imipramine, fluoxetine, and nortriptyline. Data are shown as means ± SEM (vertical bars, $n = 3$). The $IC_{50}$ values for inhibition [$^3$H]leucine binding to LeuT were 80 ± 5, 244 ± 12, 858 ± 64, and 75 ± 14 μM, respectively. (**B**) Mechanism of inhibition of [$^3$H]leucine binding to LeuT by desipramine and nortriptyline. The plot shows that desipramine and nortriptyline are not competitive inhibitors of leucine binding to LeuT. A representative experiment is shown ($n = 3$).

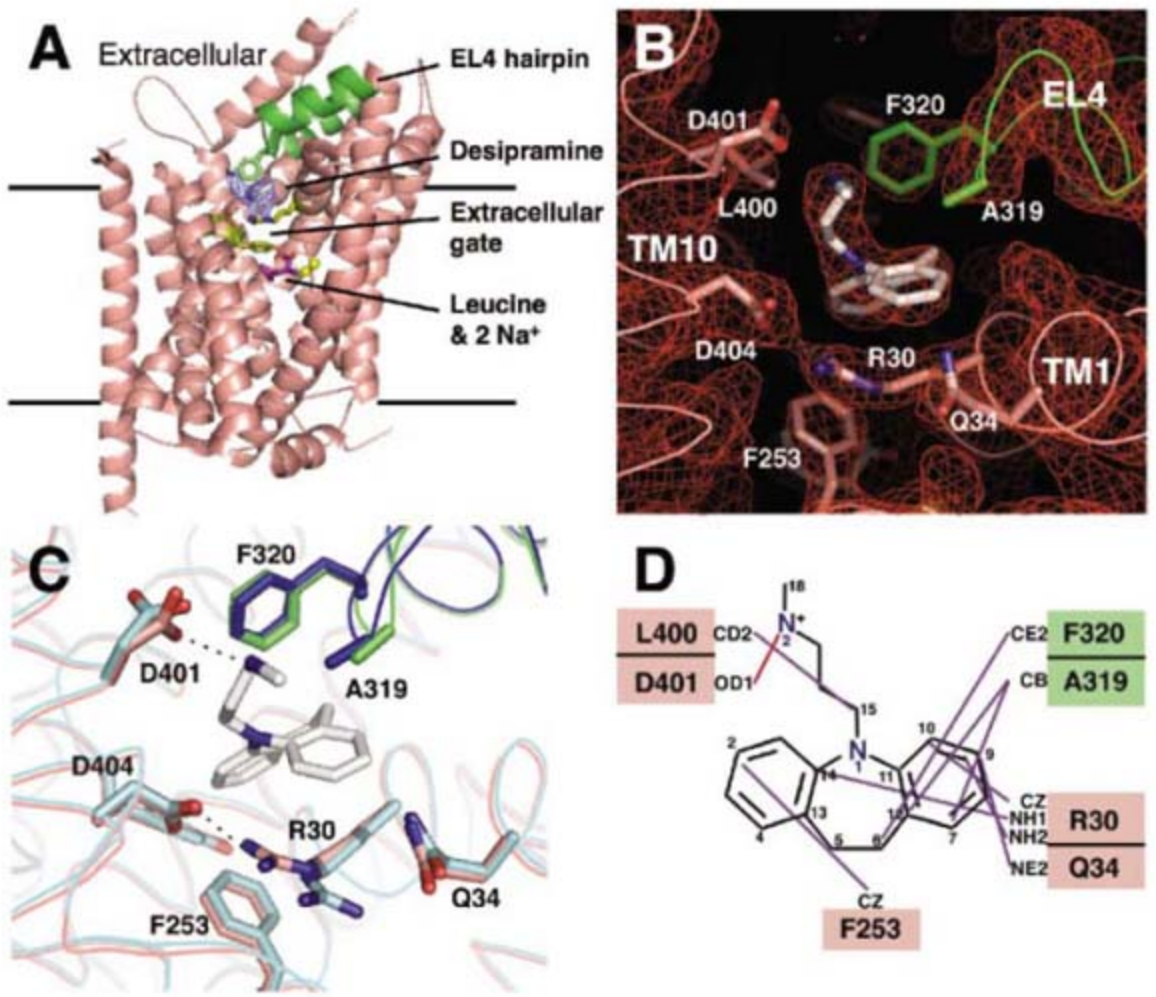


**Fig. 2.** Structure of the LeuT-desipramine complex and molecular mechanism of LeuT inhibition by desipramine. (**A**) Structure shown as ribbon diagram viewed from within the membrane plane. An $F_{obs} - F_{calc}$ map contoured at 3 σ is superimposed on the structural model. The EL4 hairpin is colored green, and the rest of the protein pink. The helices TM6 and TM11 are removed for clarity. (**B**) $2F_{obs} - F_{calc}$ map contoured at 1 σ showing the desipramine-binding site in LeuT, viewed from within the membrane plane. Residues R30, Y108, and F253 form the extracellular gate that separates the leucine substrate from the bound desipramine. (**C**) Local structural changes of LeuT induced by desipramine binding. The structure with desipramine bound is shown in pink and green, without desipramine binding in cyan and blue. When desipramine binds, the side chain of R30 rotates toward D404 and forms a salt bridge with the latter, and the EL4 hairpin, along with A319 and F320, is pushed toward to the extracellular space. (**D**) Molecular contacts between LeuT and the bound desipramine molecule. The chemical structure of desipramine is shown together with LeuT residues that are in direct contact with the drug. Residues from the EL4 hairpin are shown in the green box; residues from the rest of the protein are shown in pink boxes.

prescribed to treat depression (*12*). The molecular pharmacology of TCAs and SSRIs has been well defined, and their in vivo pharmacological effects appear to be mediated almost exclusively by serotonin- and norepinephrine-reuptake inhibition. Despite extensive investigations, however, whether the substrate-binding and drug-binding sites are overlapping and whether the drug inhibition mechanism is of a competitive nature remain controversial (*13*).

The human SERT, DAT, and NET proteins all belong to a family of transporters for amino acids and their derivatives, the neurotransmitter:sodium symporter (NSS) family (*2*–*5*, *14*). Although the dopamine transporters from human, bovine, or rat are inhibited by TCAs at an inhibition constant ($K_i$) of micromolar concentrations, the DAT proteins from *Caenorhabditis elegans* (*15*) and *Drosophila melanogaster* (*16*) are inhibited by TCAs at a $K_i$ of nanomolar and submicromolar concentrations, respectively (*17*). As bacterial NSS proteins share up to 30% sequence identity with human SERT and NET, as well as worm and fly DATs, we hypothesized that bacterial NSS proteins also have high binding affinity to TCAs and could provide opportunities for studying protein-drug interactions. We therefore chose a bacterial NSS protein, the leucine transporter (LeuT) from *Aquifex aeolicus*, to study the molecular mechanism of neurotransmitter transporter binding to TCAs (*18*). LeuT shares 20 to 25% sequence identity and 40 to 45% similarity with human neurotransmitter transporters. The crystal structure of LeuT, which was previously determined (*19*), revealed a shot glass–shaped bundle of 12 transmembrane α helices (TM1 to TM12), with a substrate leucine and two sodium ions bound at the center of the protein. The substrate-binding site is closed off from the extracellular space by a gate. There is an extracellular cavity in the protein, into which protrudes a helix hairpin formed by extracellular loop EL4.

We screened for binding of various tricyclic and other types of antidepressants to LeuT using a scintillation proximity assay (*20*). Several tricyclic compounds (imipramine, nortriptyline, protriptyline, amitriptyline, and doxepin) showed binding affinity (fig. S1), but desipramine bound LeuT most tightly, with a median inhibitory concentration ($IC_{50}$) of 80 μM (Fig. 1A). In addition, fluoxetine also showed measurable binding (fig. S1 and Fig. 1A). Desipramine was found to inhibit leucine binding to LeuT by decreasing its maximal binding capacity without changing its binding affinity (Fig. 1B); this finding indicates a mechanism that does not involve competitive inhibition. To test if desipramine binding also inhibits substrate transport, we measured the leucine transport activity of LeuT in reconstituted proteoliposomes and found that, at a concentration of 200 μM, desipramine indeed completely abolished LeuT's transport activity (fig. S2).

To investigate the molecular basis of TCA binding to LeuT, we cocrystallized the transporter with desipramine and, by directly refining the

diffraction data against the TCA-free LeuT structure (*19*) (table S1), determined the crystal structure at 2.9 Å resolution (Fig. 2A and fig. S3). The overall structure of the LeuT-desipramine complex (Fig. 2) is similar to that of the protein in the absence of desipramine (*19*), with a root mean square deviation (RMSD) of 0.2 Å for all the non-hydrogen atoms. Neither the leucine substrate nor the two $Na^+$ ions had moved. However, a 5 σ $F_{obs} - F_{calc}$ (observed and calculated structure factors) electron density peak was observed at the inner end of the extracellular cavity of the protein (Fig. 2, A and B, and fig. S3), which fits well with a desipramine molecule, an interpretation consistent with the inhibitory effect of the TCA molecule on LeuT's transport activity (fig. S2) and the evidence that desipramine is not a competitive inhibitor (Fig. 1B).

The bound desipramine molecule sits at the inner end of the extracellular cavity in LeuT with its three rings tilted at a 40° angle to the membrane plane (Fig. 2B). The "tail" of the molecule, an extended methylaminopropyl chain, projects toward the extracellular space. The desipramine molecule is separated from the substrate leucine by the extracellular gate of the transporter, which consists of residues R30, Y108, and F253 (*21*). Note that the desipramine-binding site and the leucine-binding site are nonoverlapping, but they do share F253 as a common residue. As F253 and Q34 make contact with the first and third rings of desipramine (Fig. 2, B and D, and table S2), respectively, R30 from TM1 forms cation-π interactions (*22*) with both the third desipramine ring and the phenylalanine ring of F253. On the extracellular side, desipramine is held in place by A319 and F320 of the turn of the EL4 helix hairpin, with the side chain of F320 engaging in hydrophobic interactions with the desipramine azepine ring and making contact with its tail. The desipramine tail also makes contact with residues L400 and D401 from the extracellular end of TM10. With a $pK_a$ of 10.2 (*23*) (where $pK_a$ is the acid dissociation constant) and with its nitrogen N2 atom being only 2.76 Å away from D401 (Fig. 2D and table S2), desipramine probably forms a salt bridge with the aspartate residue. In total, 393 out of 469 $Å^2$ the surface area of the desipramine molecule is buried by the protein. There is, however, still a substantial space in the protein on the extracellular side of the desipramine tail (Figs. 2B and 3A), which could accommodate the tail of other types of TCA molecules.

Although the overall LeuT structure does not change when it binds to desipramine, several residues at this binding site, as well as the backbone of the EL4 hairpin, do move (Fig. 2, A and C), by means of a typical "induced-fit" mechanism. Specifically, the guanidinium group of R30 is rotated by 170° about its Cδ–Nε bond toward D404, and two water molecules that were located between these two residues in the absence of bound desipramine (*19*) are no longer observed. As a result, R30 and D404, a pair of conserved charged residues, form a salt bridge, effectively sealing the substrate leucine off from the extracellular space. Also in TM10, the side chain of D401 is rotated toward desipramine. Finally, the bound desipramine pushes the EL4 hairpin toward the extracellular direction by ~1 Å. Coupled with a ~16° rotation of its phenylalanine ring, F320 effectively pins desipramine in place.

The crystal structure of the LeuT-desipramine complex immediately suggests a mechanism for inhibition of substrate transport by the TCA molecule (Fig. 2A and fig. S4). The desipramine molecule is held in place by a salt bridge it forms with residue D401 and by interactions with residues of the EL4 hairpin loop. Desipramine also directly binds to the extracellular gate of the transporter and locks the gate by inducing formation of a salt bridge between R30 of TM1 and D404 of TM10. The formation of this salt bridge prevents tilting of TM1, which is believed to be required for substrate release to the cytosol (*19*). Thus, no substrate transport can occur. This inhibition mechanism is in contrast from the competitive inhibition of the aspartate transporter Glt by threo-β-benzyloxyaspartate, in which the inhibitor binds partially to the substrate-binding site and concomitantly keeps the extracellular gate in an open position (*24*).

Human NSS proteins, as well as *C. elegans* and *Drosophila* DATs, share significant sequence homology with LeuT (fig. S5). Given that they all bind desipramine, we built three-dimensional homology models for the human proteins in complex with the drug by directly threading their sequences onto our LeuT-desipramine structure (Fig. 3). Both the residues of the extracellular

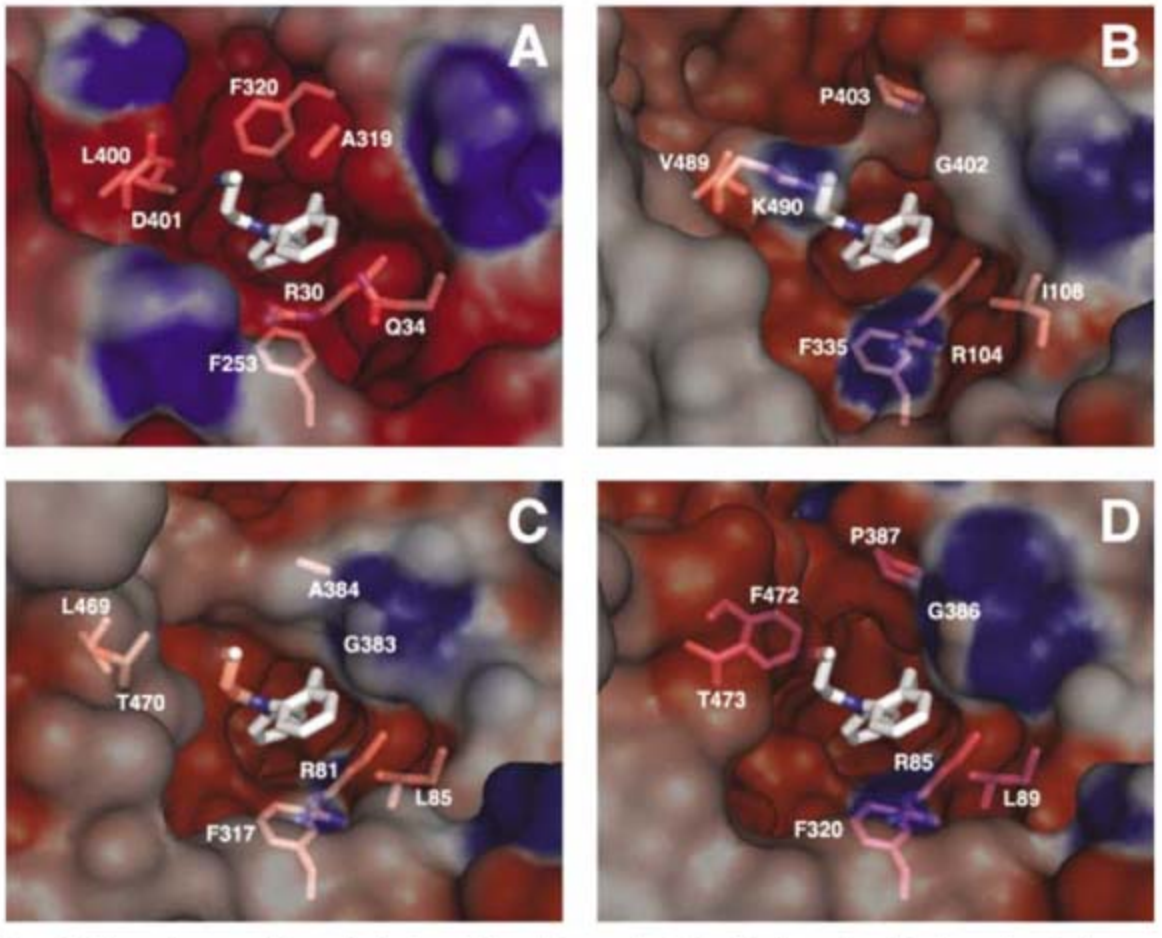


**Fig. 3.** Homology models and electrostatic surface potential of desipramine-binding sites in human SERT, NET, and DAT. (**A**) Desipramine-binding site in the LeuT-desipamine crystal structure. Homology model and electrostatic surface potential of desipramine-binding site in (**B**) hSERT, (**C**) hNET, and (**D**) hDAT, viewed from within the membrane plane. The equivalent residues of those in LeuT that are in direct contact with desipramine are indicated.

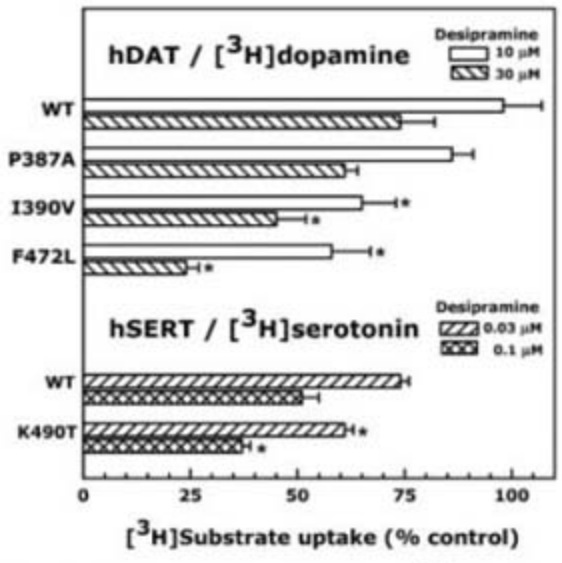


**Fig. 4.** Measurements of inhibition of [$^3$H]dopamine and [$^3$H]serotonin uptake by desipramine for human DAT and SERT mutants in HEK-293 cells. Wild-type (WT) hDAT, hSERT, and various mutant constructs are denoted on the left. Results are expressed as percentage of uptake measured with vehicle (% control). Data are shown as means ± SEM (horizontal bars, $n = 3$ to 5). *$P < 0.05$ (compared with corresponding WT at the same concentration of desipramine, one-way analysis of variance followed by Dunnett multiple comparison test for hDAT and Student's $t$ test for hSERT).

gate and the topology of the EL4 helix hairpin are conserved (fig. S5). The TCA-binding pocket in between is therefore likely to be conserved, and the homology models, which all show an acidic pocket at this position as in LeuT (Fig. 3, B to D), support this. The difference in binding affinity to TCAs among NSS proteins is likely to depend on sequence variations at the tip of the EL4 hairpin and at the extracellular end of TM10 (fig. S5). Indeed, previous experiments of both loss-of-function mutagenesis for human NET (hNET) (*17*) and gain-of-function mutagenesis (*25*) for hDAT in terms of TCA binding supported a binding site at just this position for the human NSS proteins. Thus, we hypothesized that both the desipramine-binding site and the inhibition mechanism of substrate uptake by LeuT were conserved also in the human neurotransmitter transporters.

We tested the above two hypotheses by mutating key residues at the presumed TCA-binding sites in the human neurotransmitter transporters SERT and DAT, followed by measuring their transport inhibition by desipramine in human embryonic kidney cells. The $IC_{50}$ values of desipramine for inhibiting uptake by DAT, SERT, and NET are 82,000 nM, 64 nM, and 4.2 nM, respectively (*10*). We performed gain-of-function mutagenesis in terms of desipramine binding for both hDAT and hSERT proteins by mutating their key residues to those found in the sequence of hNET, the protein with the highest affinity to desipramine. We focused on residues at the tip of the EL4 hairpin and the extracellular end of the TM10 (Fig. 2, B and D, and fig. S5). As a control experiment, we first mutated P387 in hDAT (the equivalent of F320 in LeuT) to an alanine. Because either a proline (as in *C. elegans* DAT) or an alanine (as in hNET) at this position can confer nanomolar affinity for TCAs, a proline → alanine mutation should not further increase hDAT's affinity for TCAs. Indeed, hDAT-P387A mutant showed little increase in inhibition compared with the wild-type at either 10 or 30 μM desipramine (Fig. 4), with no change in $IC_{50}$ (table S3). However, when I390 in the EL4 hairpin (equivalent of G323 in LeuT) and F472 in TM10 (equivalent of L400 in LeuT) were individually mutated into their corresponding residues in hNET (valine and leucine, respectively), the $IC_{50}$ for inhibition of [$^3$H]dopamine uptake by desipramine decreased by 63% and 79%, respectively (Fig. 4 and table S3). Similarly, in hSERT when K490 (corresponding to D401 in LeuT) was mutated into a threonine as found in hNET, a 51% decrease in $IC_{50}$ of inhibition of [$^3$H]serotonin uptake by desipramine was observed (Fig. 4 and table S3). Such gain-of-function mutagenesis data clearly demonstrate that desipramine binds to the same site in both hDAT and hSERT (Fig. 3, B and D) as it does in LeuT (Fig. 3A) and inhibits transport activity in the same manner (Fig. 2A).

Taken together, our results show that the TCA-binding site is probably conserved from bacterial to mammalian NSS proteins. Therefore, in the human $Na^+/Cl^-$-dependent neurotransmitter transporters SERT, NET, and DAT, it is likely that TCAs, as well as SSRIs, also bind between the extracellular gate and EL4 hairpin, thereby inhibiting neurotransmitter reuptake at the synapse. In combination with homology modeling (*26*) and molecular docking, the identification of this drug-binding site will allow studies on the interactions of SERT-, NET-, and DAT-specific inhibitors (*27*) with these transporters and may aid in the structure-based design of more effective neurotransmitter-reuptake inhibitors as antidepressants. As membrane proteins constitute 60 to 70% of the targets for small-molecule drugs (*28*), the strategy employed in this work can probably be used in studying protein-drug interactions for other systems.

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### Supporting Online Material

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Materials and Methods
Figs. S1 to S5
Tables S1 to S3
References


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# Cysteine Redox Sensor in PKGIα Enables Oxidant-Induced Activation


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Changes in the concentration of oxidants in cells can regulate biochemical signaling mechanisms that control cell function. We have found that guanosine 3′,5′-monophosphate (cGMP)–dependent protein kinase (PKG) functions directly as a redox sensor. The Iα isoform, PKGIα, formed an interprotein disulfide linking its two subunits in cells exposed to exogenous hydrogen peroxide. This oxidation directly activated the kinase in vitro, and in rat cells and tissues. The affinity of the kinase for substrates it phosphorylates was enhanced by disulfide formation. This oxidation-induced activation represents an alternate mechanism for regulation along with the classical activation involving nitric oxide and cGMP. This mechanism underlies cGMP-independent vasorelaxation in response to oxidants in the cardiovascular system and provides a molecular explanation for how hydrogen peroxide can operate as an endothelium-derived hyperpolarizing factor.


Oxidant molecules can cause cellular damage, dysfunction, and disease, but also play crucial roles in homeostatic maintenance of healthy cells and tissues (*1*–*3*). The modification of proteins by oxidant species with a coupled alteration in function allows cells to

sense oxidants and, therefore, to influence biological responses (*4*–*6*). Cysteinyl thiols in proteins can undergo posttranslational modifications in the presence of oxidants that are important initiators of redox signaling (*7*–*11*). Here we report that guanosine 3′,5′-monophosphate (cyclic GMP or cGMP)–dependent protein kinase (PKG), specifically the Iα isoform, is redox-sensitive and that oxidation directly activates the kinase. Oxidative stress causes interprotein disulfide bond formation between two cysteine 42 ($Cys^{42}$) residues on adjacent chains in the PKGIα homodimer complex, rendering the kinase catalytically active, independently of cGMP. Disulfide-linked enzyme has increased affinity for substrate, whereas activation by cGMP causes an increase in the maximum velocity of the enzyme-catalyzed reaction ($V_{max}$). Consistent with disulfide-mediated activation of PKGIα, hydrogen peroxide ($H_2O_2$) induces vasorelaxation of the coronary vasculature, consistent with its known function as an endothelium-derived hyperpolarizing factor (EDHF).

We found that the regulatory (R) subunits of adenosine 3′,5′-monophosphate (cyclic AMP)–dependent protein kinase form interprotein disulfides during exposure to $H_2O_2$ (*12*), which leads to activation of the enzyme (*13*). In addition, we showed that PKGIα also forms an interprotein disulfide during oxidative stress, which was reversed by the reducing agent 2-mercaptoethanol (Fig. 1). PKG contributes to the regulation of fundamental biological processes, including growth and development, gene expression, nociception, learning, behavior, synaptic plasticity, and sexual function (*14*). In the cardiovascular system, PKG regulates blood pressure, excitation-contraction coupling, and platelet aggregation and, furthermore, has roles in diseases such as atherosclerosis, abnormal cardiac and vascular remodeling, and heart failure (*15*).

PKG forms a parallel aligned homodimer, with each subunit containing both catalytic and regulatory domains. The two subunits are held together under nondenaturing conditions by a leucine zipper in the N-terminal regulatory domain, and the $Cys^{42}$ residues in aligned PKG molecules are in close proximity (*16*). PKGI has two splice-variant isoforms, Iα and Iβ, differing at their N termini in ~100 amino acids. The redox active $Cys^{42}$ is unique to the Iα isoform. This was thought to be a structurally important constitutive

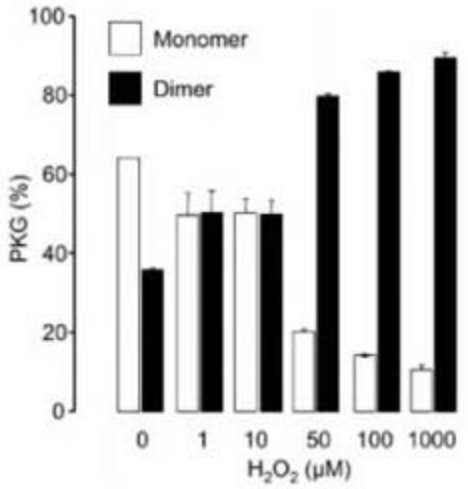


**Fig. 1.** Disulfide dimerization of PKGIα in response to $H_2O_2$. Quantitative analysis (standard error bars shown) of immunoblots (see fig. S1A), showing the proportion of monomeric and dimerized kinase after exposure to various concentrations of $H_2O_2$.

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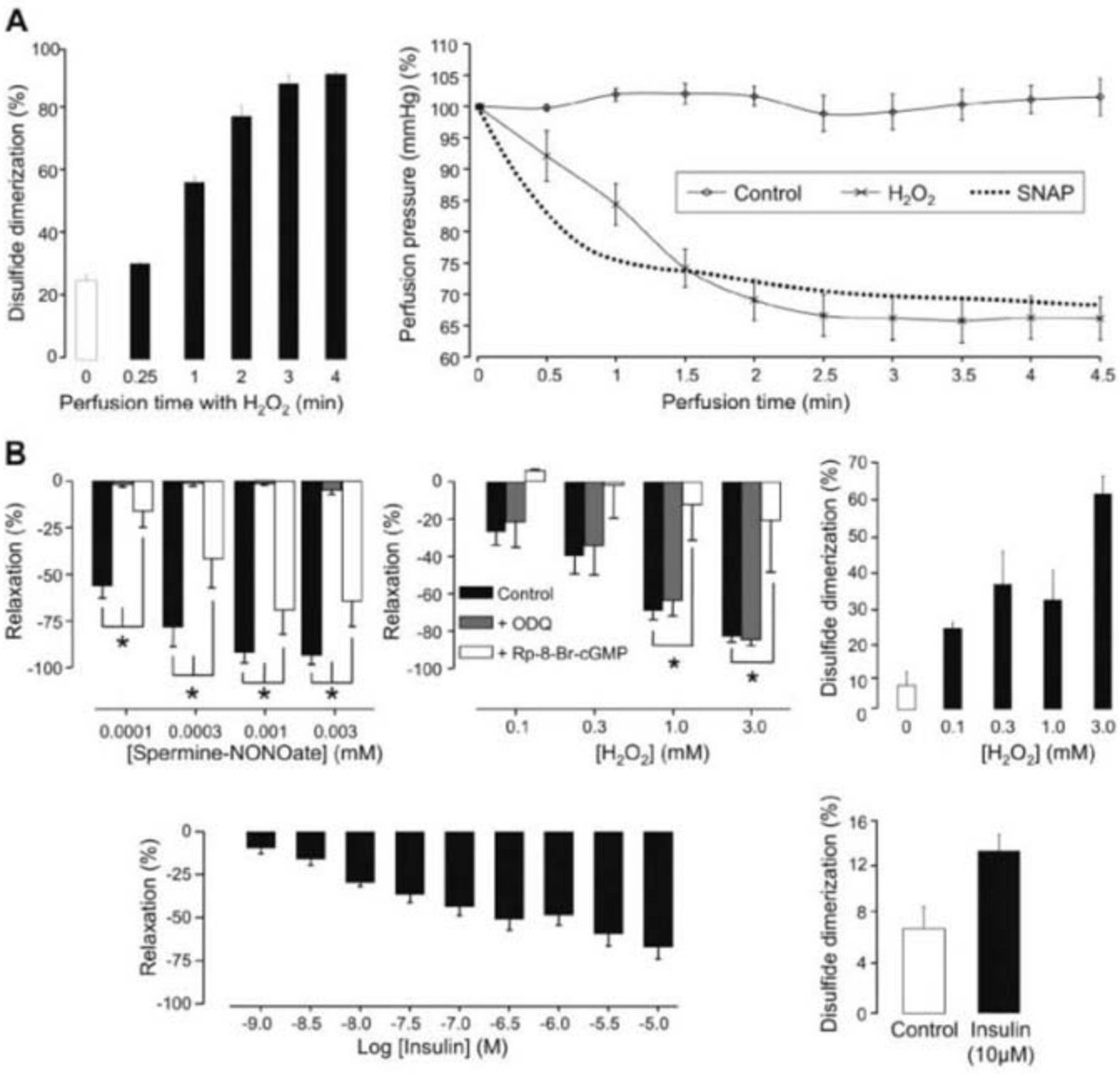



**Fig. 2.** (**A**) Effect of $H_2O_2$ on vasorelaxation and PKGIα dimerization (which occur correlatively). Proportion of PKGIα in dimerized form (left panel) or vasorelaxation (right panel) after treatment of isolated perfused rat hearts for the indicated times (standard errors shown, $r = 0.95$, $P < 0.0001$). Effect of NO donor *S*-nitroso-*N*-acetylpenicillamine (SNAP) is shown in the dotted line. (**B**) Vasorelaxation in isolated thoracic aortic rings induced by NO (top left), $H_2O_2$ (top middle), or insulin (bottom left) and dimerization of PKG by $H_2O_2$ (top right) or insulin (bottom right). Shown are the effects of inhibition by sGC (ODQ, 5 μM) or PKG (Rp-8-bromo-cGMPS, 100 μM) on NO or $H_2O_2$-mediated relaxation. *$P < 0.05$ compared with control. The degree of relaxation with the extent of disulfide oxidation correlated ($r = 0.80$, $P < 0.0001$).

disulfide (*17*), but our results suggest this is not the case, and reflects the susceptibility of this kinase to artifactual disulfide oxidation when tissue is homogenized in air. By including the thiol-alkylating agent maleimide in our preparation buffers (*18*), we trapped PKGIα in its in vivo redox state, revealing enhanced disulfide formation in tissue subjected to pro-oxidizing conditions (Fig. 1 and fig. S1A). The biochemical mapping of the interchain disulfide between $Cys^{42}$ residues on adjacent chains (*17*) is consistent with a molecular model of the N-terminal 58 amino acids of the kinase, on the basis of nuclear magnetic resonance analysis under reducing conditions (*16*) (fig. S2). PKGIα disulfide formation occurs in tissue during $H_2O_2$ treatment or in vitro (without reducing agents) on exposure to air, consistent with an initial "priming" sulfenation (-SOH) of one $Cys^{42}$ before subsequent reduction by the other on the parallel chain. $Cys^{42}$ is surrounded by basic residues, which promote ionization to the thiolate anion, rendering the cysteines reactive, which, together with proximity of ~8 Å (fig. S2) between interchain thiols, explains their susceptibility to disulfide formation.

We assessed whether nascent disulfide formation induced by $H_2O_2$ had a functional correlation. We found $H_2O_2$ treatment caused vasorelaxation in the heart, evidenced by a lowering of the coronary perfusion pressure during constant flow. Nitric oxide (NO) mediates vasodilation by binding to and activating soluble guanylate cyclase (sGC), producing cGMP which binds and activates PKG (*19*–*21*). $H_2O_2$ treatment induced time-dependent vasorelaxation (Fig. 2A), comparable to that caused by NO. $H_2O_2$-induced PKGIα disulfide formation [measured by immunoblot (Fig. 2A and fig. S1B)] correlated well with relaxation [correlation coefficient ($r$) = 0.95, $P < 0.0001$]; the half-time ($t_{1/2}$) for each was ~1 min. We reasoned that PKGIα disulfide formation may directly contribute to vasorelaxation, and this could be independent of the NO-cGMP signaling pathway. To test this hypothesis, we conducted experiments using rat thoracic aortic vessels with intact endothelium (Fig. 2B). Vasorelaxation and PKG disulfide formation were observed with $H_2O_2$ (0.01 mM to 10 mM). The NO donor, *N*-[4-[1-(3-aminopropyl)-2-hydroxy-2-nitrosohydrazino]butyl]-1,3-propanediamine (spermine NONOate, 0.1 μM to 0.1 mM) also induced relaxation (but not disulfide formation), which was significantly attenuated by pharmacological inhibition of sGC with 1H-[1,2,4]oxadiazolo[4,3-*a*]quinoxalin-1-one (ODQ, 5 μM) or PKG with Rp-8-bromo-guanosine 3′,5′-monophosphothioate (Rp-8-bromo-cGMPS, 100 μM). In contrast, $H_2O_2$-induced relaxation was inhibited by Rp-8-bromo-cGMPS, but not ODQ. Again $H_2O_2$-mediated relaxation correlated with the extent of PKGIα oxidation ($r$ = 0.80, $P < 0.0001$). However, higher concentrations of oxidant were required to produce relaxation or disulfide formation in these vessels compared with isolated hearts. The exact reason for this is unclear, but probably relates to differences in endogenous oxidant generation, peroxidase enzymes, and variable half-life and compartmentalization of oxidants. Aortic rings have a lower basal amount of PKGIα disulfide dimer than hearts, which may reflect enhanced antioxidant status, possibly explaining why higher, albeit physiological, concentrations of $H_2O_2$ concentrations are required to relax these preparations. These studies indicate that the $H_2O_2$-mediated relaxation is independent of the

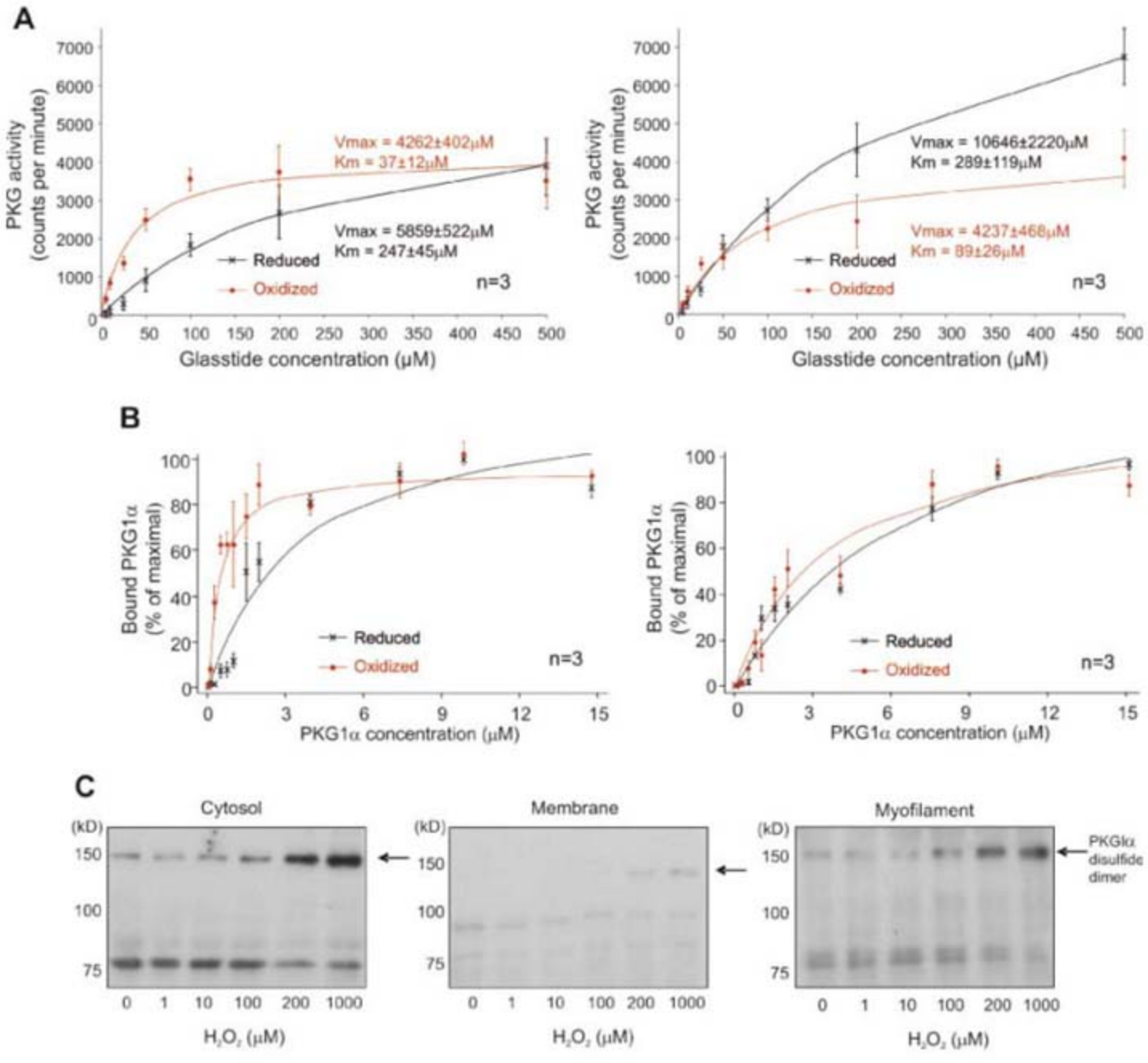
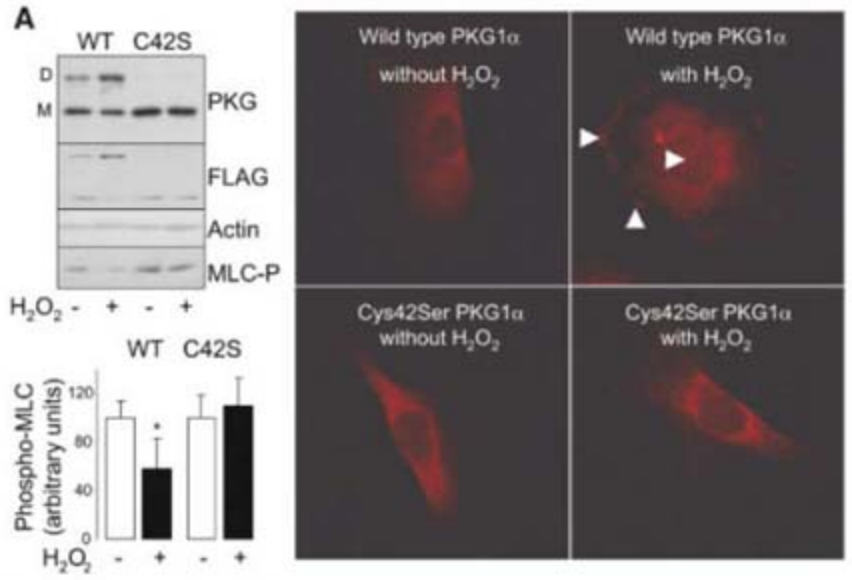
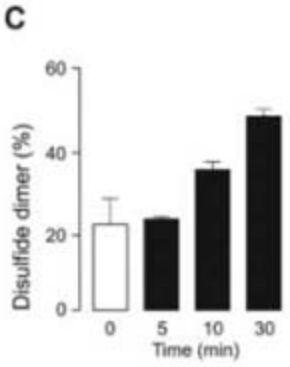



**Fig. 3.** (**A**) Effect of oxidation and cGMP on enzyme kinetics. Purified PKGIα and [$^{32}$P]ATP were used in in vitro kinase assays with Glasstide substrate. PKG with (right) and without (left) cGMP. (**B**) Effect of oxidation on the affinity ($K_d$) of PKG for RhoA substrate protein. (Left) Wild-type reduced or oxidized; (right) mutant reduced or oxidized. (**C**) Translocation of disulfide PKGIα from the cytosol to membrane or myofilament-nuclear fractions in isolated hearts treated with the indicated concentrations of $H_2O_2$.



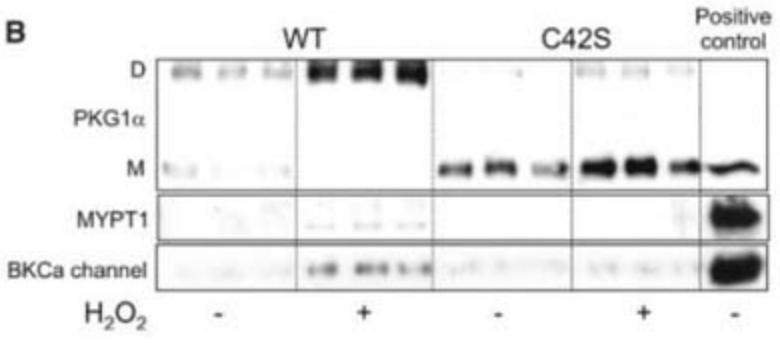




**Fig. 4.** (**A**) Effect of $H_2O_2$ on PKG substrate phosphorylation in A10 smooth muscle cells overexpressing wild-type or Cys42Ser (C42S) mutant PKGIα. (Left) FLAG-tagged Cys42Ser mutant PKGIα was overexpressed in A10 cells. D, disulfide dimer; M, reduced monomer. (Middle) FLAG-tagged wild-type PKGIα formed a disulfide bond in response to $H_2O_2$ and decreased MLC phosphorylation. $^*P < 0.05$ compared with control. Both of these $H_2O_2$-mediated events were absent in cells overexpressing Cys42Ser mutant PKGIα. (Right) Immunofluorescence was used to localize overexpressed PKG (stained with an anti-FLAG antibody) in A10 cells treated with or without $H_2O_2$. $H_2O_2$-treatment induced a cellular relocalization of wild-type PKGIα (note arrows), but this did not occur with the mutant kinase. (**B**) Affinity of wild-type or Cys42Ser PKGIα from transfected A10 cells treated with or without $H_2O_2$ for endogenous substrates. D, disulfide dimer; M, reduced monomer. Disulfide oxidized kinase associates with PKG substrates, the $BK_{Ca}$ channel and MYPT1; whereas mutant Cys42 does not. Quantitative analyses of these data are shown in fig. S3B. (**C**) Effect of insulin on PKGIα disulfide formation in A10 cells.

sGC-cGMP pathway. The existence of other EDHFs is indicated by experiments showing that vasorelaxation occurs independently of the established NO and prostacyclin pathways. In some vascular beds, $H_2O_2$ functions as an EDHF (*22*). Our observations provide a molecular explanation for how $H_2O_2$ mediates signaling via PKG without increases in cellular concentrations of cGMP. Insulin also caused disulfide oxidation in PKGIα, which is consistent with its ability to generate superoxide and $H_2O_2$ (*5*) and non–endothelium-dependent relaxation (*23*). However, the extent of insulin-mediated oxidation cannot explain the vasorelaxation induced by this hormone in our studies.

We further substantiated disulfide formation as a direct activator of recombinant PKGIα in in vitro kinase assays with the PKG substrate peptide Glasstide. cGMP treatment increased the $V_{max}$ of the kinase by 45 ± 14%, but had little effect on its Michaelis constant ($K_m$) for substrate (Fig. 3A). In contrast, disulfide oxidation had little effect on $V_{max}$, but decreased the enzyme's $K_m$ from 247 to 36 μM ($P < 0.05$). The increased affinity induced by oxidation was reversible, as dithiothreitol (DTT) treatment of the activated disulfide kinase returned activity to basal level (fig. S4A). Disulfide activation is specific to the Iα isoform, as the Iβ splice variant was not redox modulated (fig. S4B). We also determined the binding constant ($K_d$) of wild-type PKGIα or the mutant with Ser substituted for $Cys^{42}$ (Cys42Ser or C42S mutant) for its physiological substrate RhoA (Fig. 3B). Oxidation enhanced the wild-type kinase's substrate affinity 13-fold (4.6 to 0.36 μM), but had no effect when the redox cysteine was replaced with serine. In subcellular fractionation studies from hearts (Fig. 3C), $H_2O_2$ induced translocation of disulfide PKGIα from the cytosol to the membrane and myofilament fractions (compartments where principal PKG substrates are found), consistent with the oxidation-induced increase in substrate affinity. Subcellular translocation of other kinases as a result of posttranslational modifications that enhance their substrate affinity have been reported (*24*). Our observations concur with a study showing PKGIα activation by metal ion–mediated oxidation (*25*).

To test the role of oxidation in direct activation of PKGIα, we overexpressed FLAG-tagged wild-type or redox-insensitive Cys42Ser mutants in A10 smooth muscle cells. Overexpressed wild-type PKGIα, like endogenous enzyme, formed disulfide bonds following $H_2O_2$; however, the Cys42Ser mutant was unaffected (Fig. 4A). The principle mechanisms by which PKG increases vasorelaxation involve the phosphorylation of the large-conductance, $Ca^{2+}$-activated $K^+$ ($BK_{Ca}$) channel (ultimately decreasing intracellular concentration of free calcium), as well as activation of the myosin phosphatase complex (*14*). Myosin phosphatase (MYPT1) dephosphorylates the myosin light chain (MLC) to decrease smooth muscle myofilament sensitivity. We observed $H_2O_2$-induced dephosphorylation of MLC in cells expressing wild-type PKGIα (Fig. 4A). Furthermore, cells expressing redox-insensitive PKGIα demonstrated no detectable dephosphorylation of MLC. Confocal imaging of FLAG-tagged PKGIα showed that wild-type kinase relocalized in A10 cells after $H_2O_2$ treatment, but the Cys42Ser mutant did not (Fig. 4A). Wild-type or Cys42Ser mutant PKGIα was affinity-purified using 8- (2-aminoethyl)thioguanosine 3′,5′-monophosphate immobilized on agarose (8-AET-cGMP-agarose) from A10 cells treated with or without $H_2O_2$ (Fig. 4B). Affinity-purified PKGIα migrated as a disulfide dimer, shown by analysis using nonreducing SDS–polyacrylamide gel electrophoresis of cells exposed to $H_2O_2$, whereas the Cys42Ser mutant remained monomeric. The PKG substrates $BK_{Ca}$ channel and MYPT1 copurified with disulfide-oxidized wild-type kinase formed in response to $H_2O_2$, but mutant PKGIα did not form these associations. Disulfide formation of PKGIα was also induced by insulin (Fig. 4C), a hormone that is known to increase $H_2O_2$ concentration through stimulation of superoxide-generating oxidases (*5*).

We have described a pathway and mechanism by which the oxidant $H_2O_2$ directly activates PKGIα (fig. S5). All PKG isoforms have cGMP-binding cassettes (amino acids 102 to 240 in Iα), that indirectly couple kinase activity to cellular NO abundance. The amino acid sequence immediately N-terminal to these cGMP-binding sites in PKGI almost completely defines the sequence difference between α and β isoforms. The α isoform appears to have dual modes of activation, by NO-cGMP and by thiol oxidants, such as $H_2O_2$. These two sensors are side by side in the protein, seemingly optimally placed to operate as an allosteric trigger. This couples structural alterations in the kinase, either by disulfide oxidation or cGMP binding, to catalytic activity. The $Cys^{42}$ redox sensor in PKGIα is highly conserved throughout vertebrates. Consequently, this redox control of PKGIα may be a generic regulatory mechanism.

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**Supporting Online Material**
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Materials and Methods
Figs. S1 to S5
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# Common Sequence Variants in the *LOXL1* Gene Confer Susceptibility to Exfoliation Glaucoma

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Glaucoma is a leading cause of irreversible blindness. A genome-wide search yielded multiple single-nucleotide polymorphisms (SNPs) in the 15q24.1 region associated with glaucoma. Further investigation revealed that the association is confined to exfoliation glaucoma (XFG). Two nonsynonymous SNPs in exon 1 of the gene *LOXL1* explain the association, and the data suggest that they confer risk of XFG mainly through exfoliation syndrome (XFS). About 25% of the general population is homozygous for the highest-risk haplotype, and their risk of suffering from XFG is more than 100 times that of individuals carrying only low-risk haplotypes. The population-attributable risk is more than 99%. The product of *LOXL1* catalyzes the formation of elastin fibers found to be a major component of the lesions in XFG.

Glaucoma is the second most common cause of blindness worldwide (*1*). Its pathophysiology is poorly understood, and there is a compelling need for improved risk assessment and better treatment.

Glaucoma is a heterogeneous group of disorders that share a distinct optic nerve damage. In most populations, open-angle glaucoma (OAG), characterized by painless loss of vision, constitutes the majority of glaucoma cases and is defined as a progressive loss of neuroretinal rim tissue within the optic disk and consequent excavation of the optic disk with corresponding loss of visual field (*2*, *3*). OAG may be divided into primary open-angle glaucoma (POAG) and secondary glaucoma. POAG is without an identifiable cause of aqueous outflow resistance, whereas in secondary glaucoma the outflow resistance is of a known cause and in exfoliation glaucoma (XFG) it is considered to be due to the exfoliative material from which the syndrome derives its name. Exfoliation syndrome (XFS) is characterized by accumulation of abnormal microfibrillar deposits that line the aqueous bathed surfaces of the anterior segment of the eye. The prevalence of XFS increases with age, and a number of studies have pointed to a geographical clustering of XFS, although this condition is found worldwide; reported prevalence rates average about 10 to 20% of the general population over age 60 (*4*). In the Reykjavik Eye Study (*3*), 40% of individuals 80 years and older were found to have XFS. XFS is the most common identifiable cause of secondary glaucoma in most populations. A recent study (*5*) found the 15-year risk of XFS conversion to XFG to be about 60%, which is similar to results of some previous studies. XFG is characterized by rapid progression, high resistance to medical therapy, and a worse prognosis than in POAG (*6*).

Family history is an important risk factor for both POAG and XFS which, together with ethnic differences in prevalence of POAG, points to a role of genetic factors in the risk of suffering from these conditions (*7*). Three genes, *MYOC* (*8*), *OPTN* (*9*), and *WDR36* (*10*), have been found to be mutated among POAG patients. However, mutations in these genes are of moderate frequency and thus explain only a small fraction of the POAG cases (*7*).

To identify sequence variants that confer risk of glaucoma, we conducted a genome-wide association study on Icelandic patients with glaucoma, using the Illumina Hap300 chip. After quality filtering, 304,250 single-nucleotide polymorphisms (SNPs) were tested for association to glaucoma in a sample of 195 cases and 14,474 population controls [see (*11*) for a description of study groups]. The results were adjusted for relatedness between individuals and potential population stratification by the method of genomic control (*12*). Specifically, the chi-square statistics were divided by an adjustment factor of 1.055 [see (*11*) for quality-control and statistical analysis].

Overall, three SNPs achieved genome-wide significance ($P < 1.6 \times 10^{-7}$, fig. S1) and are all located within a small region in strong linkage disequilibrium on chromosome 15q24.1 (fig. S2). The strongest association with glaucoma was observed with allele T of rs2165241 (Table 1) with an odds ratio (OR) of 2.28 ($P = 2.0 \times 10^{-14}$). Also achieving genome-wide significance are allele C of rs2304719 (OR = 2.07, $P = 1.2 \times 10^{-8}$) and allele A of rs893817 (OR = 1.85, $P = 1.4 \times 10^{-7}$), but they are both substantially correlated with rs2165241 and are no longer significant ($P > 0.05$) after adjusting for the effect of rs2165241.

The 195 glaucoma cases included 90 cases classified as POAG, 75 known XFG cases, and 30 cases without a precise classification. Further analysis showed that the estimated effect of rs2165241 was weak and only marginally significant for POAG (OR = 1.36, $P = 0.040$), but very strong for XFG (OR = 3.40, $P = 4.3 \times 10^{-12}$) (Table 1). To replicate the observed association, we genotyped rs2165241 in Swedish samples including 200 POAG cases, 199 XFG cases, and 198 controls. No association was seen with POAG (OR = 0.83, $P = 0.18$), but association similar to that in the Icelandic samples was observed for XFG (OR = 3.78, $P = 3.1 \times 10^{-17}$). Combining the results from the two sample sets

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for XFG using a Mantel-Haenszel model (*13*) gave an OR of 3.62 ($P = 1.0 \times 10^{-27}$) (Table 1).

To further explore the impact of the variant, we genotyped an additional 55 Icelandic XFS cases without glaucoma. Compared to the controls, the OR is 3.18 ($P = 1.9 \times 10^{-8}$), and the frequency of rs2165241 T in XFS cases without glaucoma is similar to that in XFS cases with glaucoma ($P > 0.5$). These results indicate that the susceptibility variant tagged by rs2165241 T is a major susceptibility variant for XFS and support the notion that the variant confers risk of glaucoma mainly through XFS.

SNP rs2165241 is located in the first intron of the lysyl oxidase–like protein 1 (*LOXL1*) gene. To refine the observed association signal, we identified SNPs that are substantially correlated with rs2165241 ($r^2 > 0.2$) on the basis of the HapMap CEPH Utah (CEU) data and are not part of the Illumina Hap300 chip (table S2). Eight of those SNPs, in addition to the three best SNPs from the genome-wide scan, were successfully genotyped in all the Icelandic and Swedish XFG cases, in all the Swedish controls, and in 647 of the Icelandic controls. Also genotyped were two known nonsynonymous SNPs, rs1048661 ($Arg^{141} \rightarrow Leu$, R141L) and rs3825942 ($Gly^{153} \rightarrow Asp$, G153D), both located in the first exon of *LOXL1*. rs1048661 was identified through the dbSNP database and rs3825942 is a HapMap SNP. Both nonsynonymous SNPs showed strong association with XFG (combining Iceland and Sweden, OR = 2.46, $P = 2.3 \times 10^{-12}$ for allele G of rs1048661, and OR = 20.10, $P = 3.0 \times 10^{-21}$ for allele G of rs3825942) (Table 1). Further analysis revealed that, although rs2165241 ($P = 1.0 \times 10^{-27}$) was more significant than rs1048661 and rs3825942 individually, it was no longer significant ($P = 0.71$) after adjusting for both nonsynonymous SNPs simultaneously (tables S3 to S5); the latter was also true for the other SNPs that we typed. Results from investigating the joint effect of two nonsynonymous SNPs rs1048661 and rs3825942 are summarized in Fig. 1. The two SNPs are in substantial linkage disequilibrium ($D' = 1$), and only three of the four possible haplotypes were detected in our samples. Among the three observed haplotypes, (G, A) had the lowest estimated risk. Combining results from Iceland and Sweden, relative to (G, A), the (G, G) haplotype had an OR of 27.05 ($P = 4.0 \times 10^{-27}$) and the (T, G) haplotype had an OR of 8.90 ($P = 1.6 \times 10^{-8}$). Allele T of the intronic SNP rs2165241 was strongly associated with XFG because it effectively tagged the high-risk haplotype (G,G) ($r^2 = 0.9$). On the basis of a multiplicative model for the risks of the two risk alleles, allele G of rs1048661 has a relative risk of 3.04 = 27.05/8.90 compared to allele T, and allele G of rs3825942 has a relative risk of 27.05 compared to allele A. Notably, the haplotype (T, A) that was not seen in our samples would be predicted to have an even lower risk than (G, A). The three observed haplotypes did not show deviation from Hardy-Weinberg equilibrium in either the cases or the controls, which is consistent with the model that the risks of the two haplotypes carried by an individual multiply. Under this model, the risk of individuals carrying two copies of the high-risk haplotype (G, G) would be about 700 times the risk of those carrying two copies of (G, A) and about 2.47 times the population average risk. If the risk of the two higher-risk haplotypes, (G, G) and (T, G), could be reduced to that of (G, A), it would eliminate more than 99% of the XFG cases. Hence, the population attributable risk of the two higher-risk haplotypes is more than 99%. Sequencing of the seven exons of *LOXL1* did not identify further variants associated with the disease (table S7).

To determine if the nonsynonymous risk variants could affect the mRNA expression of *LOXL1*, we analyzed *LOXL1* expression in adipose tissue from 659 individuals with genotype data for rs1048661 and rs3825942 [microarray expression data (*11*)]. *LOXL1* expression was reduced by an estimated 7.7% with each copy carried of the risk G allele of rs1048661 ($P = 8.3 \times 10^{-7}$); this effect was significant for both sexes and did not change if the expression was adjusted for the weight of the individuals (Fig. 2). In contrast, weak positive correlation was observed between the risk G allele of rs3825942 and expression of *LOXL1* ($P = 0.034$), and this effect disappeared completely when the correlation was adjusted for the effect of rs1048661 ($P = 0.55$). The result from the microarray expression data was confirmed with real-time polymerase chain reaction for a subset of 564 of the 659 individuals (fig. S3).

The *LOXL1* gene is a member of the lysyl oxidase family of proteins that catalyzes oxidative deamination of lysine residues of tropoelastin, which leads to their spontaneous cross-linking with consequential formation of elastin polymer fibers (*14*, *15*). Elastogenesis also requires fibrillin-containing microfibrils that act as scaffolds that guide the cross-linking process and deposition of elastine (*16*). The lysyl oxidase family has five members, and these encode the prototypic LOX protein and LOX-like proteins LOXL1 to LOXL4. All five LOX family members have a

**Table 1.** Association between POAG, XFG, and XFS and rs2165241, rs1048661, and rs3825942. The association of the risk alleles of the SNP rs2165241, located in the first intron of *LOXL1*, and of the two nonsynonymous SNPs rs1048661 (R141L) and rs3825942 (G153D) with glaucoma in the Icelandic discovery case-control group, the Swedish replication case-control group, and the two groups combined. Results are shown for all glaucoma cases and for POAG cases, XFG, and exfoliation without glaucoma separately. Study population includes the number of individuals (*n*). The results include the OR, 95% confidence intervals (CI), and *P* values assuming the multiplicative model. For the Icelandic case-control group, the *P* values and CI were adjusted for relatedness as described in the methods (*11*). For the combined group, we calculated OR and *P* values using a Mantel-Haenszel model.

| Study population (*n*) | rs2165241 T | | | rs1048661 (R141L) G | | | rs3825942 (G153D) G | | |
|---|---|---|---|---|---|---|---|---|---|
| | Frq. | OR (95% CI) | *P* | Frq. | OR (95% CI) | *P* | Frq. | OR (95% CI) | *P* |
| Iceland | | | | | | | | | |
| Controls (14,474) | 0.473 | | | 0.651 | | | 0.847 | | |
| Glaucoma combined (195) | 0.672 | 2.28 (1.85–2.82) | $2.0 \times 10^{-14}$ | 0.777 | 1.87 (1.49–2.35) | $7.4 \times 10^{-8}$ | 0.936 | 2.66 (1.86–3.80) | $7.9 \times 10^{-8}$ |
| POAG (90) | 0.550 | 1.36 (1.01–1.83) | 0.04 | 0.711 | 1.32 (0.96–1.82) | 0.085 | 0.872 | 1.25 (0.81–1.91) | 0.32 |
| XFG (75) | 0.753 | 3.40 (2.41–4.81) | $4.3 \times 10^{-12}$ | 0.827 | 2.56 (1.74–3.77) | $1.8 \times 10^{-6}$ | 0.987 | 13.23 (5.59–31.29) | $4.1 \times 10^{-9}$ |
| XFS no glaucoma (55) | 0.740 | 3.18 (2.12–4.76) | $1.9 \times 10^{-8}$ | 0.789 | 2.02 (1.32–3.09) | $1.3 \times 10^{-3}$ | 0.982 | 10.10 (4.02–25.36) | $8.5 \times 10^{-7}$ |
| Sweden | | | | | | | | | |
| Controls (198) | 0.535 | | | 0.682 | | | 0.879 | | |
| Glaucoma combined (399) | 0.649 | 1.61 (1.26–2.05) | 0.00016 | 0.737 | 1.31 (1.00–1.70) | 0.048 | 0.929 | 1.79 (1.19–2.70) | 0.0052 |
| POAG (200) | 0.488 | 0.83 (0.63–1.09) | 0.18 | 0.638 | 0.82 (0.61–1.10) | 0.19 | 0.863 | 0.87 (0.57–1.31) | 0.49 |
| XFG (199) | 0.813 | 3.78 (2.77–5.14) | $3.1 \times 10^{-17}$ | 0.834 | 2.39 (1.72–3.34) | $2.7 \times 10^{-7}$ | 0.995 | 27.28 (11.44–65.07) | $9.1 \times 10^{-14}$ |
| Combined | | | | | | | | | |
| Controls (14,672) | | | | | | | | | |
| Glaucoma combined (594) | | 1.96 (1.67–2.29) | $1.3 \times 10^{-16}$ | | 1.59 (1.35–1.89) | $7.5 \times 10^{-8}$ | | 2.20 (1.69–2.85) | $3.4 \times 10^{-9}$ |
| POAG (290) | | 1.04 (0.85–1.28) | 0.67 | | 1.02 (0.83–1.27) | 0.83 | | 1.04 (0.78–1.39) | 0.81 |
| XFG (274) | | 3.62 (2.87–4.55) | $1.0 \times 10^{-27}$ | | 2.46 (1.91–3.16) | $2.3 \times 10^{-12}$ | | 20.10 (10.80–37.41) | $3.0 \times 10^{-21}$ |

similar exon structure consisting of seven exons, five of which (exons 2 to 6) exhibit strong homology and encode the C-terminal catalytic domain of these proteins. The sequence difference between the *LOX* genes resides mainly in exon 1, which encodes pro-peptide that is, after the attachment of *LOXL1* to the scaffolding structure, cleaved off for catalytic activation of the enzyme. Several studies have demonstrated that the *LOXL1* pro-peptide binds to both tropoelastine and fibulin-5 and that these interactions are essential for directing the deposition of the enzyme onto elastic fibers (*14*, *16*).

The pathology of XFS is characterized by chronic accumulation of abnormal fibrillar material in the anterior segment of the eye, leading to numerous clinical complications apart from secondary glaucoma development. From analysis of the XFS material, it has been proposed that XFS arises from abnormal aggregation of elastin microfibrillar components (elastic microfibrillopathy) produced by various intraocular cell types (*6*, *17*). Although a role for LOXL1 in the formation of the extracellular matrix of the eye has not been documented, LOXL1 expression is detected in ocular tissues such as lamina cribrosa, lens epithelium, cornea, ciliary muscle, and trabecular meshwork, all of which may be involved in extracellular matrix formation (*18*–*20*) [data accessible at NCBI GEO database (*11*)]. We demonstrate here the association of two coding SNPs, rs1048661 and rs3825942, with XFG that leads to an amino acid change at position 141 (Arg→Leu) and 153 (Gly→Asp), respectively, both of which are located in the N-terminal pro-peptide. Based on the functional role of the pro-peptide, these alterations could affect both the catalytic activity of the protein through modifications of pro-peptide cleavage and the binding to substrates like tropoelastine and fibulin-5. In addition, we demonstrate that the risk allele of rs1048661 associates with lower expression levels of the *LOXL1* mRNA in adipose tissue. This effect could be mediated through its linkage disequilibrium to noncoding regulatory elements or through its own effect on mRNA stability or processing, as previously documented for both synonymous and nonsynonymous coding mutations in genes such as *DRD1*, *MDR1*, and *OPRM1* (*21*–*23*). Assuming a similar regulatory network for *LOXL1* expression in adipose and ocular tissues, these data suggest that low levels of *LOXL1* expression could predispose to XFS.

Ocular tissue was not available to us to study the effect of the risk alleles on the expression of *LOXL1*, and we considered it unlikely that we could obtain such tissue from a sufficiently large number of individuals to do a meaningful study. Our assumption was that it would be difficult to predict what tissue would best reflect ocular tissue in this respect and that any tissue expressing the gene in an easily detectable amount would serve our purpose as well as other such tissues. *LOXL1* is expressed at very low levels in the blood, and thus we were unable to determine whether the risk variants affect its expression. Hence, we analyzed RNA from adipose tissue because samples from several hundred individuals were available to us. In adipose tissue, the expression of *LOXL1* is decreased by 7.7% per risk allele of rs1048661 (R141L), which is a small change and not necessarily biologically meaningful, although in a late-onset disease it could be relevant. It is, however, notable that the risk allele of rs3825942 (G153D), the variant that confers the greater risk, has no effect on LOXL1 expression.

In summary, we have shown in two independent study groups that two nonsynonymous changes in exon 1 of the *LOXL1* gene on chromosome 15q24.1 confer risk to XFG, possibly through XFS. In Iceland and Sweden, the high-risk haplotype is very common with an average frequency of about 50% in the general population. About 25% of individuals in the general population are homozygous for the haplotype with the highest risk, and their risk of suffering from XFG is estimated to be about 700 times that of individuals carrying only the low-risk haplotype, or about 2.47 times that of the population average. Jointly, the two nonsynonymous changes account for more than 99% of all XFG cases. The product of the *LOXL1* gene modifies elastin fibers that are a major constituent of the intraocular lesions in XFG. As to other forms of glaucoma, after removing the SNPs in the *LOXL1* region, the genome-scan Q-Q plots for POAG and glau-

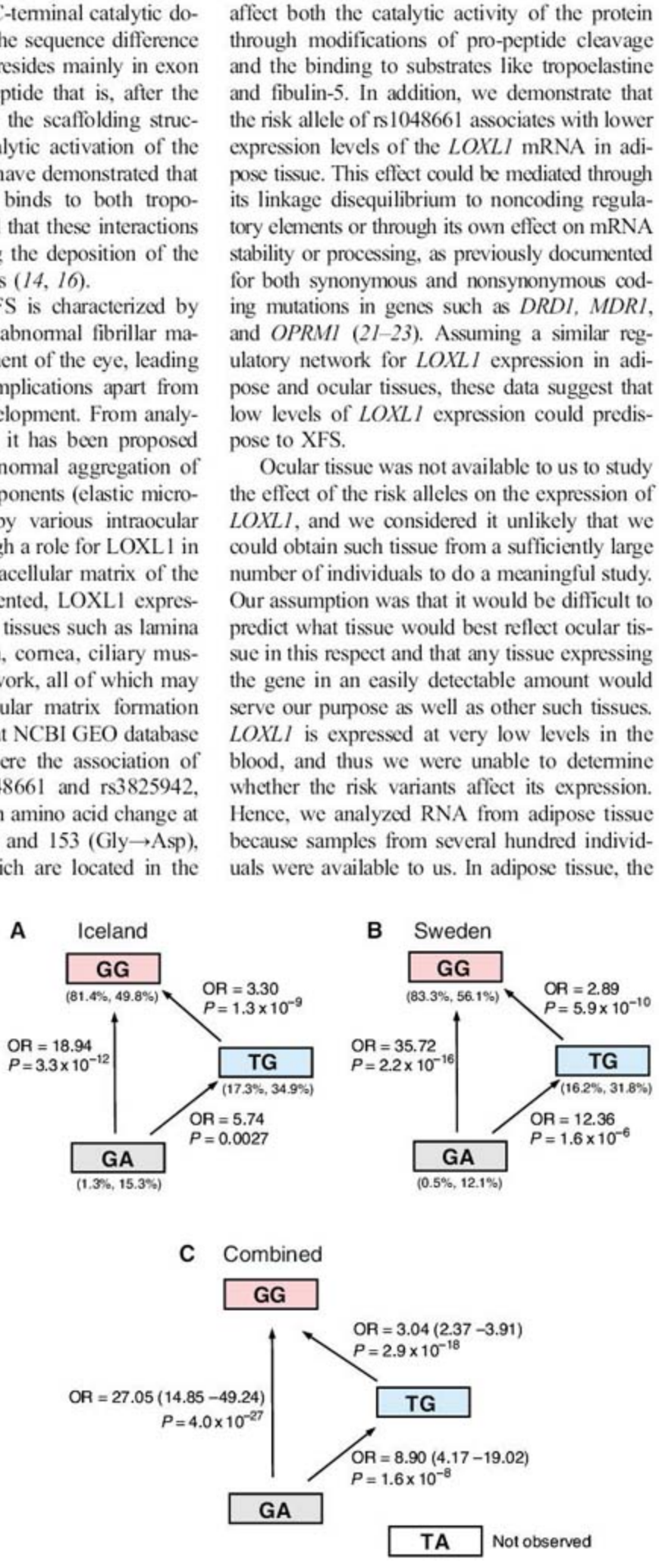


**Fig. 1.** Association of XFG with haplotypes formed by the two nonsynonymous SNPs, rs1048661 and rs3825942. Pairwise comparison of the risk of carrying the three haplotypes (G, G), (G, A), and (T, G), formed by the alleles of the two nonsynonymous SNPs rs1048661 (R141L) and rs3825942 (G153D). Arrows indicate the comparison of two haplotypes, and the OR is that of the haplotype the arrow is pointing to relative to the haplotype from which it originates. The results are shown for (**A**) Iceland and (**B**) Sweden separately, and (**C**) for the two populations combined. For (A) and (B), estimated haplotype frequencies in cases and controls are given in parentheses below each haplotype. For (C), the Mantel-Haenszel model was used to compute ORs and the 95% confidence intervals in parentheses. The haplotype formed by the protective alleles, (T, A), is not observed in the Icelandic or the Swedish case-control groups.

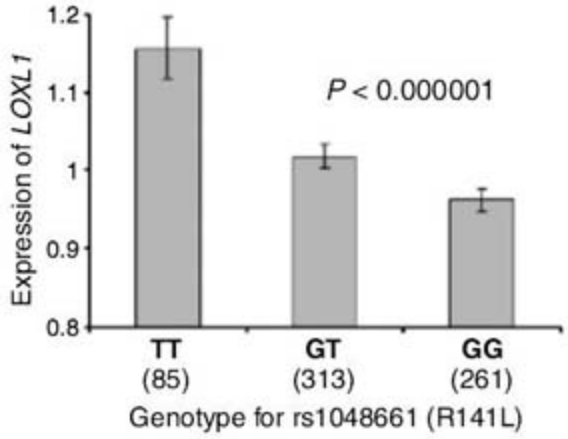


**Fig. 2.** Correlation between genotypes of rs1048661 (R141L) and expression of *LOXL1* in adipose tissue. Expression of *LOXL1* measured in adipose tissue from 659 individuals by means of a microarray for the different genotypes of the nonsynonymous at-risk SNP rs1048661 (R141L). The expression of *LOXL1* is shown as 10exp (average MLR), where MLR is the mean log expression ratio and the average is over individuals with a particular genotype. Regressing the MLR values on the number of copies of the at-risk variant G that an individual carries, we find that the expression of *LOXL1* is reduced by an estimated 7.7% with G allele carried ($P$ = 0.00000083). The effect of age and sex is taken into account by including an Age × Sex term among the explanatory variables in the regression. The error bars indicate the SEM. The correlation remains if the expression is adjusted for weight of the individual by including body-mass index as an explanatory variable ($P$ = 0.0000013). Similar results are obtained if the 275 males and the 384 females are analyzed separately ($P$ = 0.00029 and $P$ = 0.00060, respectively).

coma overall cannot be distinguished from that resulting from random noise (fig. S1b), which suggests that POAG may be a more complex disease than XFG.

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### Supporting Online Material

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Materials and Methods
Figs. S1 to S3
Tables S1 to S7
References


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# The *Fusarium graminearum* Genome Reveals a Link Between Localized Polymorphism and Pathogen Specialization


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We sequenced and annotated the genome of the filamentous fungus *Fusarium graminearum*, a major pathogen of cultivated cereals. Very few repetitive sequences were detected, and the process of repeat-induced point mutation, in which duplicated sequences are subject to extensive mutation, may partially account for the reduced repeat content and apparent low number of paralogous (ancestrally duplicated) genes. A second strain of *F. graminearum* contained more than 10,000 single-nucleotide polymorphisms, which were frequently located near telomeres and within other discrete chromosomal segments. Many highly polymorphic regions contained sets of genes implicated in plant-fungus interactions and were unusually divergent, with higher rates of recombination. These regions of genome innovation may result from selection due to interactions of *F. graminearum* with its plant hosts.


*Fusarium*, a genus of plant pathogenic fungi, causes diseases that affect most species of cultivated plants, including root and stem rots, blights, and wilts (*1*). *F. graminearum*, which causes Fusarium head blight (FHB) disease on wheat and barley, is a leading cause of economic loss in these crops (*2*). In addition to reducing seed mass and quality, the fungus contaminates grain with toxic metabolites that are a threat to human health (*3*). *Fusarium* species also can directly infect humans, causing localized necrotic diseases (*4*) and invasive infection, especially in immunocompromised individuals (*5*).

The *F. graminearum* genome was whole-genome shotgun sequenced by paired-end sequencing of plasmid, Fosmid, and bacterial artificial chromosome (BAC) clones. The resulting assembly totals 36.1 Mb and displays high sequence quality and continuity. Nearly all (99.8%) of the assembly was anchored to the four chromosomes by genetically mapping markers derived from the genome sequence (*6*), and an initial set of 11,640 genes was predicted (table S1 and SOM text). Functional categories for the predicted genes were inferred by the presence of conserved InterPro domains (*7*) and were compared with those found in genomes of the related fungi, *Neurospora crassa*, *Magnaporthe grisea* and *Aspergillus nidulans*. The *F. graminearum* genome has greater numbers of genes for several protein categories, including predicted transcription factors, hydrolytic enzymes, and transmembrane transporters (Fig. 1 and table S2).

The *F. graminearum* genome has few high-identity duplicated sequences, fewer by at least a factor of 15 than other related fungi, including *Saccharomyces cerevisiae* (table S3 and SOM text). Only a few gene pairs originated from recent duplications (fig. S1 and table S4), and we identified only two small families of transposons (table S5 and SOM text). *F. graminearum* differs from other filamentous fungi because it is homothallic (self-fertile) and rarely out-crosses, which limits the opportunity to acquire new repeats (*2*). In some ascomycetous fungi, including *F. graminearum*, the lack of repetitive sequence is due to a genome-wide defense system known as repeat-induced point mutation (RIP) (*8*). RIP identifies duplicated sequences (*9*) and introduces C:G to T:A transition mutations in both copies during the sexual cycle; this mutational bias was observed in *F. graminearum* transposons (tables S6 and S7 and SOM text).


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To experimentally confirm the activity of RIP, we examined the stability of transgenically introduced repeats of a hygromycin phosphotransferase (*hph*) gene during sexual and asexual development. Although cultures derived from asexual spores maintained drug resistance, 42% of cultures derived from ascospores, which are formed during the sexual cycle, were sensitive to hygromycin (table S8), and 99% of mutations found in the *hph* gene were C to T point mutations, most at CpA sites (tables S9 and S10), indicating that repetitive sequences are frequently mutated by a RIP-like process during meiosis. Ascospores are important for FHB infection (*2*) and, being homothallic, *F. graminearum* may undergo meiosis and produce ascospores with greater frequency because it is unconstrained by the necessity for finding a compatible mate. An increased opportunity for meiosis may impact the genome by increasing the frequency of RIP, allowing it to play a more central role.

We compared the assembly of strain PH-1 with ~0.4-fold coverage of whole-genome shotgun sequence from a second strain of *F. graminearum*, GZ3639. We identified 10,495 single-nucleotide polymorphisms (SNPs) between the two strains and mapped SNP positions along each chromosome. Because the GZ3639 data does not cover every base in the genome, SNP densities were normalized to the number of high-quality base alignments (*7*). For this normalized data set, SNP densities ranged from 0 to 17.5 SNPs per kb. We found that the distribution of SNPs is biased, because 25% of SNPs are found within 5% of the genome sequence, and 50% of SNPs are within 13% of the genome sequence. Regions exhibiting high SNP densities were clustered along each chromosome (Fig. 2). In particular, all telomere proximal regions displayed very high densities of SNPs and contained the vast majority of the highest SNP density windows. In addition to chromosome ends, three chromosomes were found to have one or two large interstitial regions of high SNP density. Whereas telomeres are well established in many species as sites of sequence variation and rearrangement (*10*–*12*), the presence of discrete interstitial regions of high diversity in addition to the subtelomeres is striking. One simple explanation is that these sites may reflect ancestral telomere locations resulting from an ancestral chromosome fusion. Although *F. graminearum* has four chromosomes, related fungi with similar

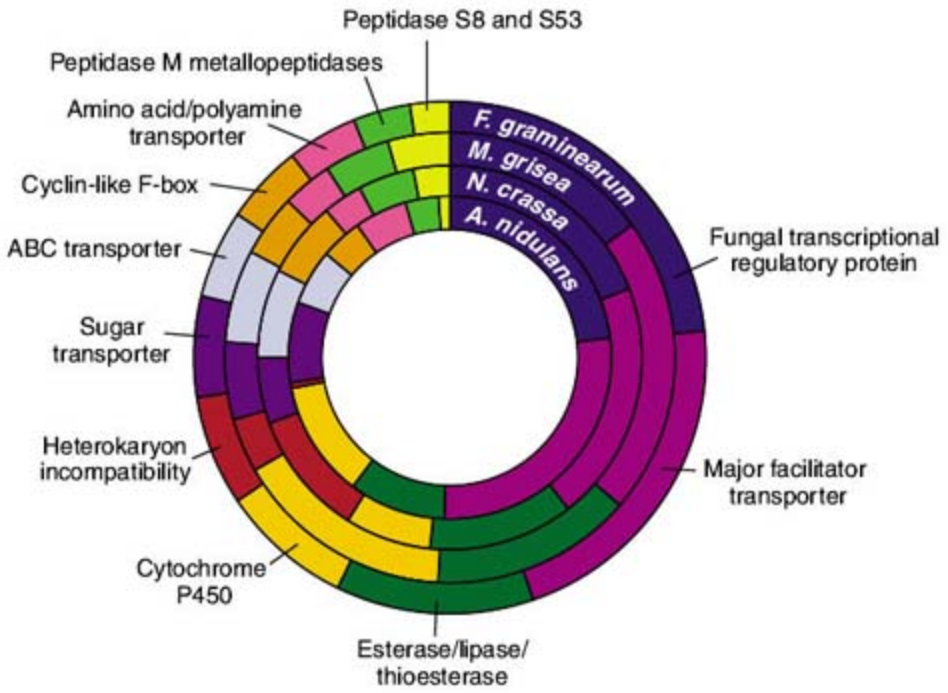


**Fig. 1.** Functional classification of *F. graminearum* proteins and comparison to other fungi. Displayed Interpro gene categories were found to have at least 50% greater gene abundance in *F. graminearum* than in *N. crassa*. Representative gene numbers for *M. grisea* and *A. nidulans* are also shown. Each circle displays the relative fraction of genes represented in each of the categories for each genome. For a full list of Interpro categories, see mips.gsf.de/genre/proj/fusarium/Search/Catalogs/searchIprComp.html.

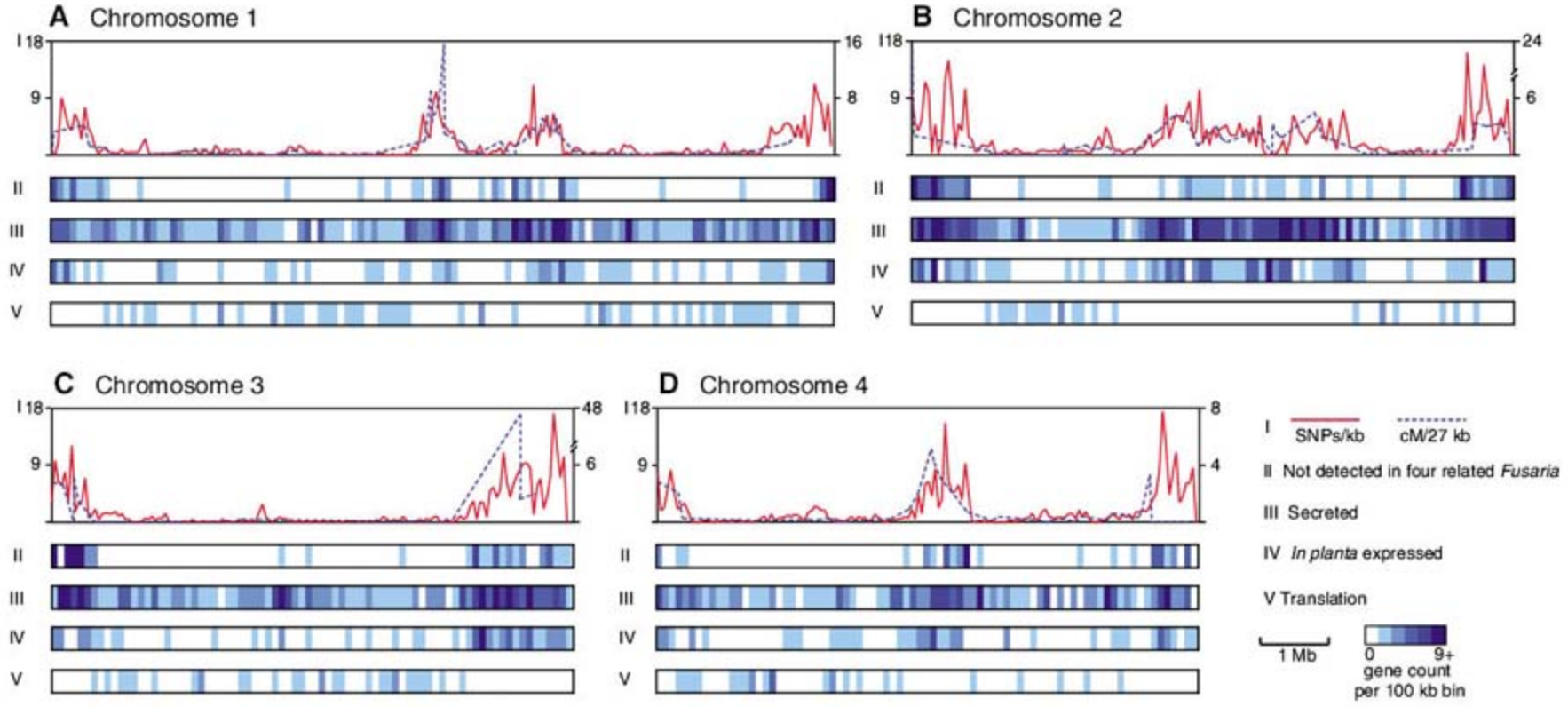


**Fig. 2.** Correlation of high SNP regions with recombination and gene sets. The four *F. graminearum* chromosomes are shown proportional to size. Panels (**A**) to (**D**) represent chromosomes 1 to 4, respectively. (I) Distribution of SNPs (red lines) and recombination rate (blue dashed lines) for 50 kb non-overlapping windows across each chromosome (*x* axis). SNPs are plotted on the left *y* axis as the number of SNPs per kb of high-quality aligned bases (*7*). Recombination rate [cM/27 kb (*6*)] is plotted on the right *y* axis. (II to V) Gene counts for the following gene sets (*7*) are shown with relative density shading for tiled 100-kb windows: (II) Genes found in *F. graminearum* but absent from four related *Fusarium* species. (III) Secreted proteins. (IV) Genes expressed specifically in planta. (V) Proteins involved in translation.

genome size, including *F. verticillioides*, *F. oxysporum*, and *F. solani*, have many more, ranging from 9 to >17. All closely related species in the *F. graminearum* species complex, as well as *F. culmorum*, also have four chromosomes, which indicates that if chromosome fusion occurred, it was not a recent event.

The regions of highest SNP density were significantly correlated with the regions of highest recombination (0.55, $P = 1.2 \times 10^{-13}$), similar to correlations of SNP distribution or nucleotide diversity with recombination frequency observed in humans and *Drosophila* (*13*, *14*). Additionally, regions of high SNP density have significantly lower G+C content than the rest of the genome (–0.43, $P = 1.1 \times 10^{-8}$). The low G+C content of internal regions further supports the idea that these regions may represent ancestral telomeres.

To determine whether high diversity SNP regions evolved recently, we examined the sequence divergence of genes in these regions. We compared *F. graminearum* coding regions to those resulting from a low coverage (4X) assembly of *F. verticillioides* (*7*). Comparing the best matches for *F. graminearum* proteins from high and low SNP density regions (top and bottom quartiles) to the *F. verticillioides* assembly revealed that proteins from the highest SNP density regions have fewer putative orthologs compared with the rest of the genome and that these orthologs share lower identity (*7*). Although variation in the local mutation rate is expected to produce a correlation between polymorphism and divergence, more polymorphisms were found in high SNP regions than predicted on the basis of divergence (table S13), and the ratio of synonymous to nonsynonymous polymorphisms is higher than that of less diverse regions ($\chi^2$ value = $3.7 \times 10^{-7}$) (table S14).

Blast analysis (*7*) identified 704 genes as specific to *F. graminearum*, and these show significant enrichment in the high-density SNP regions ($P = 4.5 \times 10^{-15}$). We also compared *F. graminearum* with the closely related *F. asiaticum*, *F. boothii*, *F. culmorum*, and *F. pseudograminearum* using genomic DNA hybridizations to a *F. graminearum* microarray (*15*) and identified 382 genes that are *F. graminearum* specific. These genes were overrepresented (by a factor of 2.7) in the high-density SNP regions ($P = 3.4 \times 10^{-34}$). These data further demonstrate that genomic regions exhibiting the highest intraspecific variability also exhibit the highest interspecific variability.

*F. graminearum* genes specifically expressed during plant infection—including predicted secreted proteins, major facilitator transporters, amino acid transporters, and cytochrome P450s—are all overrepresented in high SNP density regions (Fig. 2, table S14, and SOM text). Conversely, genes predicted to be highly conserved, such as nuclear encoded mitochondrial genes or genes involved in translation, are underrepresented in regions of high diversity (table S15 and SOM text).

Comparison of gene expression of *F. graminearum* infection on barley and under varied nutritional culture conditions (*7*, *15*) identified 408 genes as exclusively expressed during barley infection. These genes are highly enriched in the high-SNP-density regions ($P = 7.4 \times 10^{-15}$), and 31% are predicted to be secreted, representing enrichment by a factor of 3 over the genome as a whole (table S14 and SOM text). Four of these genes have similarity to known virulence factors, and another 32 genes are predicted plant cell-wall degrading enzymes (table S16). Among these enzymes are xylanases, which degrade xylan, the major hemicellulose portion of monocot cell walls, pectate lyases, which cleave pectin, another essential component of plant cell walls and cutinases, enzymes that hydrolyze cutin polyesters that coat all outer plant surfaces. Such enzymes may function in the penetration and maceration of plant tissues and for the acquisition of nutrients from plant polymers (*16*) and may be involved as effector molecules that trigger host-plant defense responses (*17*). The high genetic diversity of this group of genes suggests that the fungus has a great capacity for adaptability and genetic change during its interaction with even this single host species.

The completed genome of *F. graminearum* allowed us to identify distinct regions of high diversity. We found that these regions are enriched for infection-related genes, which may allow the fungus to adapt rapidly to changing environments or hosts. Recognition of these high-diversity areas of the genome focuses the direction of future work toward those regions that may have the greatest potential in elucidating the dynamics of host pathogen interactions.

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### Supporting Online Material

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# The Perception of Rational, Goal-Directed Action in Nonhuman Primates

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Humans are capable of making inferences about other individuals' intentions and goals by evaluating their actions in relation to the constraints imposed by the environment. This capacity enables humans to go beyond the surface appearance of behavior to draw inferences about an individual's mental states. Presently unclear is whether this capacity is uniquely human or is shared with other animals. We show that cotton-top tamarins, rhesus macaques, and chimpanzees all make spontaneous inferences about a human experimenter's goal by attending to the environmental constraints that guide rational action. These findings rule out simple associative accounts of action perception and show that our capacity to infer rational, goal-directed action likely arose at least as far back as the New World monkeys, some 40 million years ago.

A central characteristic of human action perception is the capacity to read beneath the surface appearance of behavior. When someone acts, we make inferences about their goals and intentions by referencing each action against a backdrop of environmental constraints. In humans, this capacity appears around the first year of life. For instance, Gergely

and colleagues (*1*) showed that when 14-month-old infants watched an experimenter use her head to illuminate a box, infants imitated this precise action only if the experimenter's hands were free to move and could have been used to illuminate the box; if the experimenter's hands were occupied, and could not be used, then the infants used their hands. Infants most likely inferred that since the experimenter could have used her hands, but used her head instead, the head must confer some advantage for illuminating the box. These results, and others (*2*, *3*), suggest that human infants assess whether an agent's actions are rational by evaluating how the intervening environmental circumstances constrain the achievement of a target goal; as such, they infer properties of mental life that are not transparent from the surface appearance of behavior. Presently unclear, however, is whether this capacity is the product of human evolution or uniquely human pedagogy, or rather is shared with other animals.

Behavioral and neurophysiological studies show that nonhuman primates attend to subtle details of the surface properties of actions, including differences in the gestures used to achieve a goal (*4*–*6*). Further, there is suggestive evidence that animals go beyond the mere consequences of actions, distinguishing intentional from accidental consequences (*6*–*7*). For example, captive chimpanzees show more heightened signs of frustration when an experimenter appears to tease intentionally by offering and then taking away food as opposed to offering and then clumsily dropping food—two events with the same consequences, that is, the failure to obtain food (*6*). In addition, cotton-top tamarins are more likely to cooperate with a partner who gives food altruistically than with a partner who gives food as an accidental by-product of otherwise selfish behavior (*7*). Moreover, Hare and Tomasello (*5*) found that chimpanzees can use information about an agent's apparent intentions to find hidden food; in other contexts, however, chimpanzees have considerable difficulty understanding intentional cues by humans (*8*–*11*). Thus, these results leave three questions unanswered: (i) To what extent can animals spontaneously use information about an agent's apparent intentions to make inferences about their goals? (ii) Are their inferences based solely on the surface appearance of behavior, as opposed to information about whether actions are rational with regard to current environmental constraints? (iii) What is the phylogenetic distribution of these capacities, especially among our closest living relatives, the monkeys and apes?

To begin addressing these questions, we adopted a broad comparative perspective, conducting experiments on three nonhuman primate species (cotton-top tamarins, rhesus macaques, and chimpanzees), representing the three major groups (New World monkeys, Old World monkeys, and apes). We tested all three species in largely the same way, but due to housing conditions and sample sizes, there were some differences (*12*).

In experiment 1, we asked whether members of these species perceive actions as intentional and accidental, and critically, use this information when making inferences about the apparent goal of a human agent. We used a forced-choice method designed to measure subjects' spontaneous foraging behavior in response to actions performed by a human experimenter. During each trial, an experimenter presented subjects with two potential food containers, performed an action on one, and then allowed the subject to select one of the containers. In the intentional condition, the experimenter reached directly for and grasped the container. In the accidental condition, the experimenter flopped his hand onto the container with palm facing upwards in a manner that appeared, from a human perspective, accidental and non–goal-directed (*13*). If nonhuman primates fail to distinguish between intentional and accidental actions when making inferences about others' goals, attending to the mere association of the hand and container, then they should show the same pattern of searching in both conditions—that is, approach the experimenter-contacted container. However, if they distinguish between intentional and accidental actions, then they should selectively inspect the container targeted by the experimenter's intentional action but not that targeted by accidental action.

Based on the statistical methodology used in our other studies of rhesus behavior, we elected to use one-tailed tests in this work, too. All three species inspected the intentionally targeted container a greater proportion of time than the accidentally targeted container: tamarins [$F(1,9)$ =

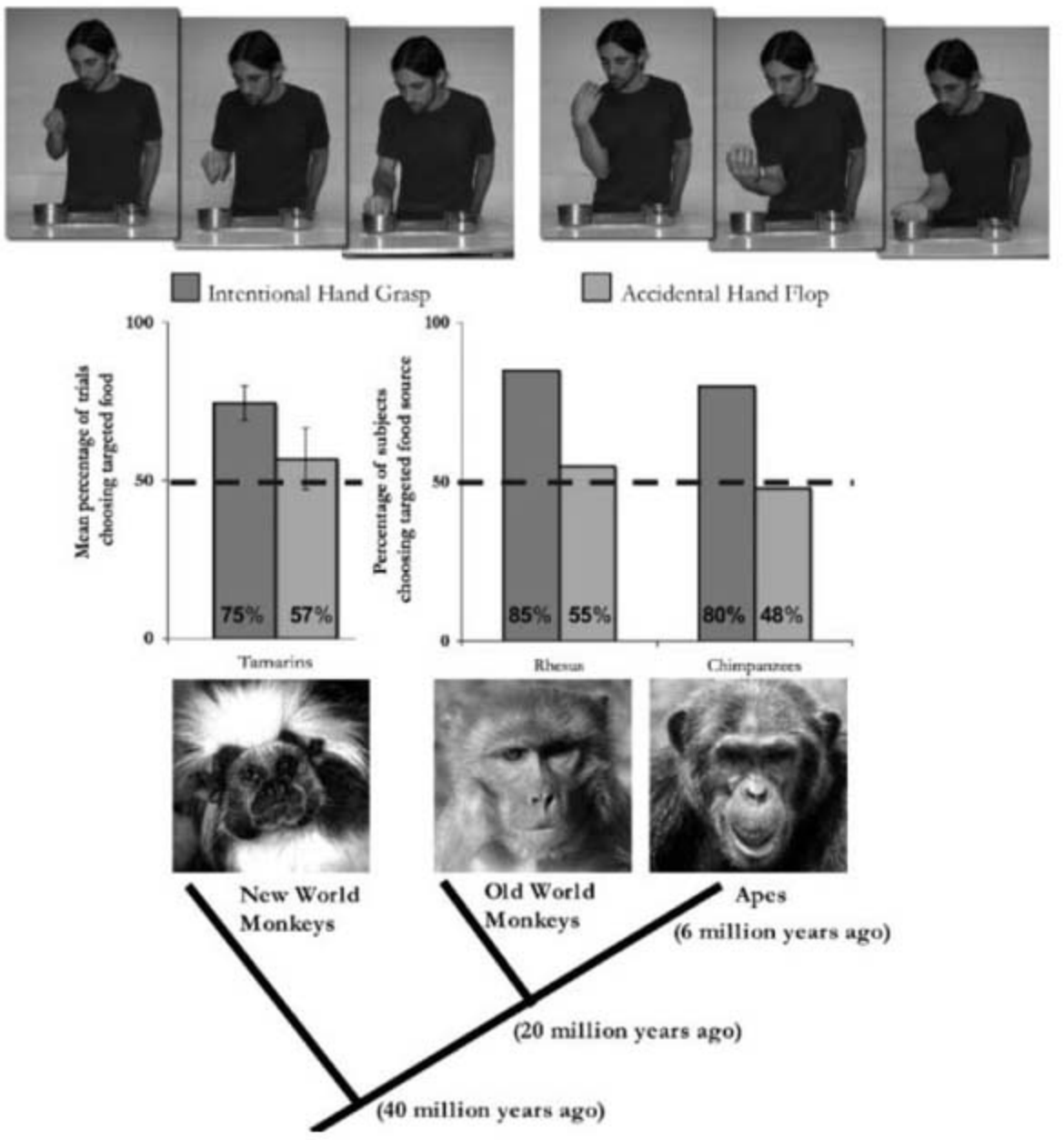


**Fig. 1.** Performance for choosing the container targeted by the intentional (dark gray) versus accidental (light gray) actions by tamarins, rhesus, and chimpanzees. The tamarin data illustrate the mean percentage of trials (±SEM). See fig. S1 for the mean percentage of trials as measured by both looking and grasping behaviors. The rhesus and chimpanzee data illustrate the percentage of subjects choosing the container targeted by each action type. The dashed line indicates chance performance.

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3.57, $P = 0.05$]; rhesus [$\chi^2(1,N=40)=4.29$, $P=0.02$]; chimpanzees (Wilcoxon signed ranks test: $z = -2.02$, $P = 0.02$). All species selectively inspected the targeted container after observing the intentional action (Fig. 1): tamarins [$t(9) = 4.45$, $P = 0.001$]; rhesus (17 out of 20 subjects; binomial probability: $P = 0.001$); chimpanzees (20 out of 25 subjects; binomial probability: $P = 0.002$). In contrast, none of the species selectively inspected the targeted container after the accidental action: tamarins [$t(9) = 0.70$, $P = 0.25$]; rhesus (11 out of 20 subjects; binomial probability: $P = 0.41$); chimpanzees (12 out of 25 subjects; binomial probability: $P = 0.50$). Thus, tamarins, rhesus monkeys, and chimpanzees spontaneously distinguish between intentional and accidental actions and use this information to make inferences about others' goals. These results provide further support for studies of chimpanzees (*5*, *6*) and extend the pattern to tamarins and rhesus. In addition, they suggest that these three species go beyond the mere association of contact or the attention drawn to one container to correctly infer the agent's target goal.

How do these species distinguish between intentional and accidental actions: Do they do so solely on the basis of the surface appearance of behavior, or, like humans, do they interpret actions in relation to the broader environment in which they occur? That is, did the subjects tested in experiment 1 judge the hand grasp as goal-directed and the hand flop as accidental because grasping and flopping actions are automatically interpreted as intentional and accidental, respectively? Alternatively, did they evaluate the hand flop as accidental because, in this particular situation, the experimenter could have used the more rational grasping action?

In experiment 2, we asked whether these three species integrate information about the surface properties of an action with the environmental constraints facing the agent in order to make inferences about rational, goal-directed action. We presented subjects with an experimenter performing very similar actions under two contrasting environmental circumstances. In the first condition, the experimenter touched one of the containers with his elbow while the associated hand was occupied ("hand-occupied"); in the second contrasting condition, the experimenter performed the same elbow touch action while the associated hand was free ("hand-empty"). One-half of both the chimpanzee and rhesus subjects observed the experimenter perform the hand-occupied elbow touch while holding an object in his acting hand only; the other hand was placed behind his back. The other half of the subjects observed the experimenter perform the action while holding an object in both hands. If nonhuman primates evaluate actions merely on the basis of surface appearance (e.g., the association between the elbow and the container), then they should show the same pattern of searching in both the hand-occupied and hand-empty conditions because the surface properties of the actions are very similar, including, especially, the structure of the final point of contact. However, if these species take into account the environmental constraints facing the experimenter, then only the hand-occupied condition should be perceived as a rational, goal-directed action; given that the experimenter's acting hand was occupied at the moment of gesturing, his elbow provides an alternative means to both indicate and contact the target goal. Accordingly, the hand-empty condition would not be perceived as a rational, goal-directed action because at the time, the experimenter could have used his unoccupied acting hand to grasp and indicate the target container (as in the intentional condition of experiment 1), leaving the subject uncertain as to the target goal. Therefore, subjects should not infer that the experimenter's goal was to contact the box with the potentially concealed food.

We note that our target species do not naturally use their elbows to indicate or draw attention to objects or events in their environment, and nor have they been trained to either use their elbows in an indicative manner, or respond to this action. This condition therefore also explores their capacity to use an indicative, but unfamiliar gesture, to make inferences about goal-directed action under specific environmental constraints.

All species inspected the targeted container a greater proportion of the time after observing the hand-occupied versus the hand-empty action: tamarins [$F(1,24) = 2.60$, $P = 0.06$]; rhesus [$\chi^2(1,N = 64) = 10.47$, $P < 0.001$]; chimpanzees (Wilcoxon signed ranks test: $z = -1.87$, $P = 0.03$). All species selectively inspected the targeted container in the hand-occupied condition (Fig. 2): tamarins [$t(9) = 4.31$, $P = 0.001$]; rhesus (28 out of 32 subjects; binomial probability: $P < 0.001$); chimpanzees (19 out of 25 subjects; binomial probability: $P = 0.007$). In contrast, none of the species selectively inspected the targeted container in the hand-empty condition: tamarins [$t(14) = 0.29$, $P = 0.39$]; rhesus (16 out of 32 subjects; binomial probability: $P = 0.57$); chimpanzees (11 out of 25 subjects; binomial probability: $P = 0.35$). Thus, subjects used the elbow action as a cue to find hidden food only when the experimenter's acting hand was occupied, and thus unavailable for gesture and action. One possibility is that in the hand-empty condition, subjects attended primarily to the experimenter's hand in expectation of rational, goal-directed action; when this did not occur, the elbow cue could have gone unnoticed or been dismissed as irrational and accidental. In contrast, when the experimenter's hands were occupied, subjects may have been particularly attentive to other body parts because they became viable alternatives for rational, goal-directed action. These results [along with other evidence recently presented (*14*, *15*)] suggest that all these primate species—and possibly other animals as well—go beyond the surface appearance of behavior as well as their own experiences acting on or indicating objects when making inferences about others' goals. Like humans, they evaluate others' actions with respect to environmental constraints imposed on the agent.

It is interesting that these species perceived the hand-occupied elbow touch as goal-directed given that it is impossible to pick up an object with one's elbow. The most likely explanation for

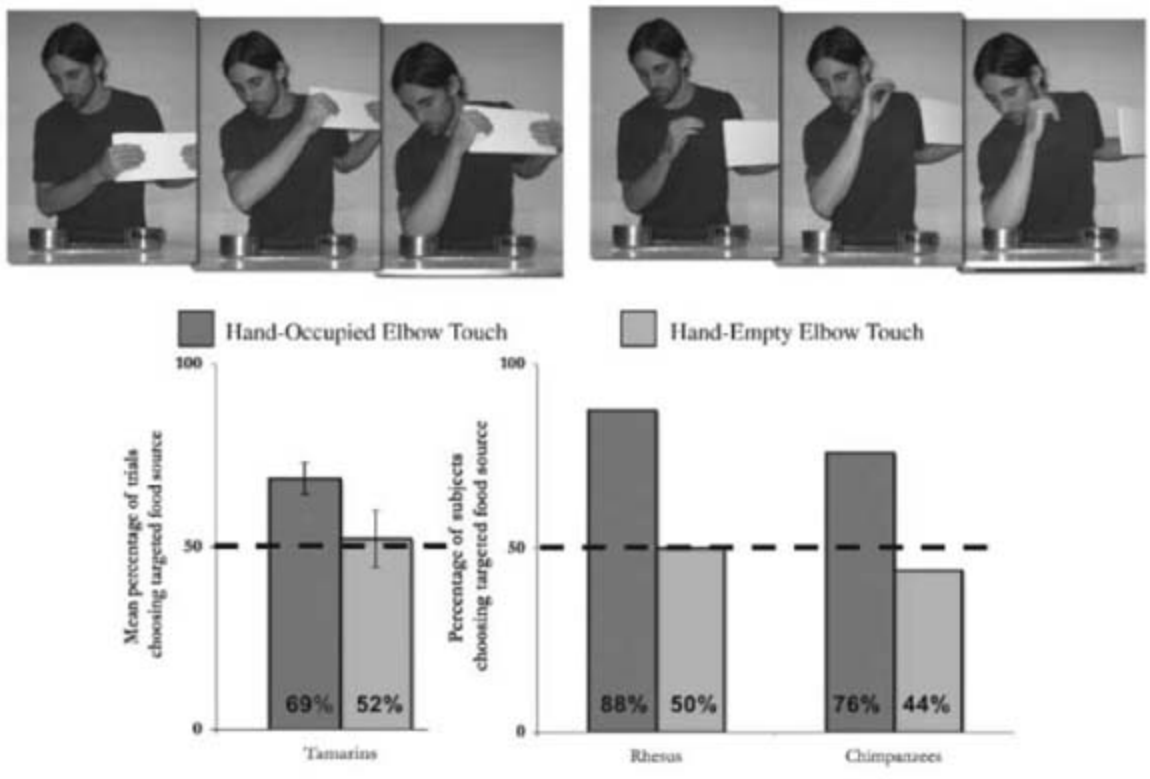


**Fig. 2.** Performance for choosing the container targeted by the hand-occupied (dark gray) versus hand-empty (light gray) elbow actions by tamarins, rhesus, and chimpanzees. The tamarin data illustrate the mean percentage of trials (±SEM). See fig. S1 for the mean percentage of trials as measured by both looking and grasping behaviors. The rhesus and chimpanzee data illustrate the percentage of subjects choosing the container targeted by each action type. The dashed line indicates chance performance.

this pattern is that subjects inferred that the experimenter's goal was to contact or indicate the presence of food, rather than to grasp the food.

Given enough time and leisure, human adults are free to consider almost any action as irrational. For instance, the subjects in our study, and the human infants in previous studies (*1*), perceived uncharacteristic elbow and head actions as rational and goal-directed provided that the experimenter's hands were occupied; this response obtained even though the experimenter could have dropped the object and then performed the more efficient hand action. Similarly, our subjects showed the same pattern of searching regardless of whether the hand-occupied elbow touch was performed with both hands occupied or with one hand behind the back; the latter condition is of interest because the experimenter could have performed the grasping action with the hand that was behind his back. We suggest that at the initial stage of action analysis, rational actions are defined in terms of current and immediate constraints on the agent. Thus, at the moment the experimenter indicates the target object with his elbow while one hand is occupied and the other rests behind his back, the subject's initial interpretation is that both of the experimenter's hands are unavailable. This amendment to current theoretical models of action perception makes sense of both human (*1*) and nonhuman animal results.

The present results appear to contrast with previous studies indicating that chimpanzees have difficulty using human pointing, looking, or many other communicative gestures to find a hidden reward. In particular, in an object choice task, in which an experimenter conceals a piece of food in one of two or more hiding locations, several studies reveal that captive chimpanzees (*8*–*11*), as well as other primates (*16*, *17*), generally fail to use a human agent's pointing gesture and direction of eye gaze to correctly infer the location of hidden food. We cannot precisely pinpoint the exact nature of the differences between these studies and the present one. However, support for the chimpanzee results is aided by the converging evidence from tamarins and rhesus based on similar methods.

Our results support three primary conclusions that bear on the origins and nature of action perception, restricted to these three primate species, but potentially generalizable to other closely and distantly related species. First, the species tested are highly sensitive to the surface properties of observed actions. All three species selectively inspected a potential food source targeted by the experimenter's action after observing the hand grasp action, but not after observing the hand flop action. A low-level explanation in terms of attention via eye gaze, body position, or other social cues cannot explain these results given that in both experiments, contact with the target container and the experimenter's visual attention were held constant, but subjects' patterns of search differed.

Second, results show that tamarins, rhesus, and chimpanzees distinguish between goal-directed and accidental behavior based on the relation between actions and environmental constraints. This finding has notable implications for cognitive and neurobiological models of action understanding. Physiological studies of macaque mirror neurons in area F5 of the premotor cortex indicate that these cells activate both when the subject acts and when this same subject observes another acting in the same way (*4*). On the basis of these activation patterns, theorists have suggested that the mirror neuron system plays a critical role in action perception, where organisms interpret the actions of others by appealing to their own actions (*4*, *18*). Current neurobiological models of the mirror neuron system often state that action understanding consists of mapping the surface properties of observed actions onto the observer's motor system. Our results show, however, that action perception cannot be based solely on a mechanism that analyzes the surface properties of actions. In experiment 2, subjects distinguished between hand-occupied and hand-empty elbow touches, even though these actions have similar surface properties and are not within the repertoire of actions performed by these species. Thus, action perception must also consist of a mechanism that evaluates action means in relation to goals, and places this analysis into a broader context that entails constraints imposed by the current environmental situation. As a result, some system must supplement the mirror neuron circuitry to provide a fuller account of action perception in primates.

Third, the psychological mechanisms underlying the socio-cognitive abilities of animals have been widely debated, often acting as a proxy for larger debates between supporters of associative as opposed to more mentalistic accounts of animal learning and behavior. Associative models classically explain behavior as a result of direct reinforcement history—for example, the capacity to understand actions as goal-directed may be the product of learning, acquired by forming associations between observed actions and the objects that they target. Such models cannot explain the present findings without modification. In experiment 2, all three species perceived an elbow touch as goal-directed, despite presumably having little or no experience witnessing other agents manipulate objects with their elbow when their hands were occupied, and certainly no experience with other conspecifics indicating objects with their elbows; consequently, there was no opportunity to form an association between this action and object-directed outcomes. Thus, we suggest that nonhuman primates' ability to perceive actions as goal-directed extends beyond these associative mechanisms, drawing upon inferences about an agent's goals in the context of particular environmental constraints.

In sum, our results show that both closely and distantly related primate species distinguish between goal-directed and accidental actions when making inferences about another individual's apparent goals. Furthermore, they do so by evaluating the rationality of the action in relation to the constraints of the situation. The fact that these results hold across three different primate species, and that the methods entail spontaneous, nontrained responses, adds substantially to the robustness of our findings and their implications for thinking about the evolution of action perception. We conclude that our capacity to perceive rational, goal-directed actions is not uniquely human, having evolved at least as far back as the New World monkeys, some 40 million years ago.

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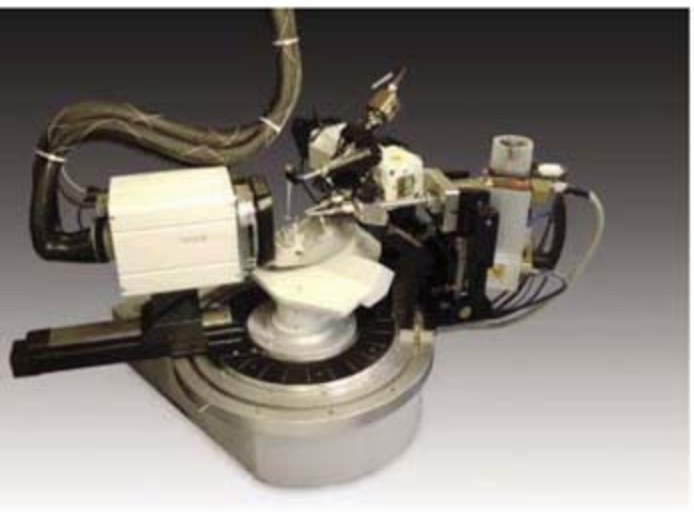

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- **Molecular Dissection of Macroautophagy**
  (Yoshinori Ohsumi / Zvulun Elazar / Tamotsu Yoshimori / Sharon Tooze / Eeva-Liisa Eskelinen)
- **Macroautophagy: From Components to Regulation and Back**
  (Michael Thumm / Maria Isabel Colombo / Tomas Neufeld)
- **Macroautophagy and Organelle Degradation**
  (Rod Devenish / Victor Shengkan Jin / Suresh Subramani)
- **Specialized Autophagy**
  (Idan van der Klei / William Dunn / David Goldfarb / Erwin Knecht / Hui-Ling Chiang)
- **Autophagy, Polyubiquitin and Aggregopathies**
  (Eiki Kominami / David Rubinsztein / Ralph Nixon / Terje Johansen)
- **Autophagy in Native and Acquired Immunity**
  (Vojo Deretic / Christian Münz / Martine Biard-Piechaczyk / Akiko Iwasaki / Hebert Virgin)
- **Autophagy and Disease**
  (Andrew Thorburn / Patrice Codogno / Eileen P. White)
- **Autophagy, Cell Death and Aging**
  (Adi Kimchi / Kevin M. Ryan / Jayanta Debnath)

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**BIOLOGY OF 14-3-3 PROTEINS**
Feb 24-29, 2008
Crowne Plaza
Ventura, CA
Chairs: Tohru Ichimura & Anthony Muslin
Vice Chair: Carol Mackintosh

- **14-3-3 Protein Function in Transcription and Translation**
  (Alastair Aitken / Mihiro Yano)
- **Structure and Target Recognition of 14-3-3 Proteins**
  (*David Klein* / Tomas Obsil / Raymond Hui / Min Li / Bengt Hallberg)

**visit the frontiers of science... go to a gordon conference! (www.grc.org)**

- **Proteomics of 14-3-3 Ligands**
  (*Carol MacKintosh* / Heiko Hermeking / Tohru Ichimura / Amparo Acker-Palmer)
- **14-3-3 Proteins in Signal Transduction and Cell Cycle Regulation**
  (*Alastair Aitken* / Deborah Morrison / Guri Tzivion)
- **14-3-3 Proteins in Metabolism**
  (*Jan Szopa* / David Klein / Carol MacKintosh / Steven Huber)
- **14-3-3 Proteins in Genetics and Development**
  (*Robert Ferl* / Paul van Heusden)
- **14-3-3 Proteins in Plant Physiology**
  (*Steven Huber* / Robert Ferl / Jan Szopa / Patriza Aducci)
- **14-3-3 Proteins in Cancer, Neurodegeneration, and Cardiovascular Disease**
  (*Gri Tzivion* / Satoshi Inoue / Mong-Hong Lee / Haian Fu / Markus Otto / Anthony Muslin)

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## NEW! BIOLOGY OF ACUTE RESPIRATORY INFECTION

Mar 9-14, 2008
Four Points Sheraton / Holiday Inn Express
Ventura, CA
Chair: Joseph P. Mizgerd
Vice Chair: Jay K. Kolls

- **Perspectives of Respiratory Infection: Patients, Populations, and Ecosystems**
  (Antoni Torres / Marc Lipsitch / Albert D.M.E. Osterhaus)
- **Bacterial Acute Respiratory Infections**
  (Elaine I. Tuomanen / Alice S. Prince / Joanne Engel / Duncan C. Krause / Keith P. Klugman)
- **Viral Acute Respiratory Infections**
  (Yoshihiro Kawaoka / Kanta Subbarao / Jeffrey S. Kahn)
- **Recognizing Microbes in the Lungs**
  (Douglas T. Golenbock / Shizuo Akira / Chad Steele / Jo Rae Wright / Lester Kobzik)
- **Coordinating Lung Immune Responses**
  (Theodore J. Standiford / Shawn J. Skerrett / Yong-Jun Liu)
- **Antimicrobial Immune Effector Mechanisms**
  (Paul B. McCray / Michelle S. Swanson / Arturo Zychlinsky / Marco Colonna / Stephen J. Turner)
- **Vaccination**
  (David L. Woodland / Denis W. Metzger / John J. Treanor)
- **Inflammatory Injury**
  (Terrence M. Tumpey / R. Stokes Peebles / Thomas R. Martin / Claire M. Doerschuk / Michael A. Matthay)
- **Antimicrobial Drugs and Resistance**
  (Dan I. Andersson / Robert S. Daum / Frederick G. Hayden)

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## BIOMOLECULAR INTERACTIONS & METHODS
### Protein Interaction Dynamics: Theory, Method, & Practice

Jan 13-18, 2008
Four Points Sheraton / Holiday Inn Express
Ventura, CA
Chairs: Michelle Arkin & Colin Kleanthous
Vice Chairs: Karen Fleming & Gideon Schreiber

- **Macromolecular Machines and Assemblages**
  (*Jeff Hansen* / Craig Peterson / P. John Hart / Jack Corriea)
- **Advances in Physical Methods**
  (*Linda Nicholson*)
- **Single-Molecule Dynamics**
  (*Justin Molloy* / Taekjip Ha / David Colquhoun)
- **Enzyme Dynamics**
  (*Steve Benkovic* / Sharon Hammes Schiffer / Rama Ranganathan / Vern Schramm)
- **Protein-Drug Dynamics**
  (*Jeffery Kelly*)
- **Protein Fluctuations and Function**
  (*Ruth Nussinov* / Michele Vendruscolo / Charalampos Kalodimos / Lila Gierasch)
- **Conformational Heterogeneity and Natively Disordered Proteins**
  (*Peter Tompa* / Richard Kriwacki / Laurence Barron / Vladimir Uversky)
- **Protein Network Dynamics**
  (*Stephen Michnick* / Andre Levchenko / Klaus Hahn / Dev Sidhu)
- **Keynote Address: Design of Protein-Protein Interactions**
  (*Michelle Arkin* / David Baker)

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## CHROMATIN STRUCTURE & FUNCTION

May 11-16, 2008
Il Ciocco
Lucca (Barga), Italy
Chair: Peter B. Becker
Vice Chair: Robert Kingston

- **Nucleosome Fibres**
  (*Karolin Luger* / Jon Widom / Daniela Rhodes / David Tremethick / Oliver Rando)
- **Chromatin Assembly and Repair**
  (*Daniela Rhodes* / Karolin Luger / Genevieve Almounzi / Craig Peterson / Steve Henikoff / Bas van Steensel)
- **Dynamic Chromatin Transitions**
  (*Craig Peterson* / Brad Cairns / Toshio Tsukiyama / Geeta Narlikar / Tom Owen-Hughes)
- **Histone Modifications and Signalling**
  (*Bryan Turner* / David Allis / Shelley Berger / Tony Kouzarides / Michael Grunstein / Jerry Workman / Yang Shi)
- **Active Chromatin**
  (*Jerry Workman* / Jane Mellor / Ali Shilatifard / Danny Reinberg / Ingrid Grummt)
- **Silent Chromatin**
  (*Jeannie Lee* / Robin Allshire / Shiv Grewal / Danesh Moazed / Thomas Jenuwein / Ramin Shiekhattar / Sharon Dent)
- **Balancing the Genome**
  (*Steve Henikoff* / Mitzi Kuroda / Barbara Meyer / Edith Heard / Jeannie Lee)
- **Programming and Reprogramming Functional States**
  (*Ingrid Grummt* / Bryan Turner / Amanda Fisher / Jürg Müller / Renato Paro / Rudi Jaenisch / Yi Zhang)
- **Chromosomes and Nuclear Organisation**
  (*Genvieve Almouzni* / Thomas Cremer / Wendy Bickmore / Peter Fraser / Susan Gasser)

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## COLLOIDAL, MACROMOLECULAR & POLYELECTROLYTE SOLUTIONS

Feb 3-8, 2008
Four Points Sheraton / Holiday Inn Express
Ventura, CA
Chairs: Ralph H. Colby & Esin Gulari
Vice Chair: Lynn M. Walker

- **Polyelectrolyte Theory**
  (*Marshall Fixman* / Andrey Dobrynin / Michael Rubinstein)
- **Colloid Assembly**
  (*John Walz* / Michael Solomon / Darrell Velegol / Steve Foulger)
- **Polyelectrolyte Complexes and Overcharging**
  (*Phil Pincus* / Boris Shklovskii / Serge Lemay)
- **Surfactant Structures**
  (*Phil Sullivan* / Paul Callaghan / Suzanne Fielding / Kate Stebe)
- **Biological Polyelectrolyte Complexes**
  (*Paul Dubin* / Manfred Schmidt / Federico Bordi)
- **Novel Macromolecules**
  (*Patrick Warren* / Lynn Loo / Julia Kornfield / Nick Abbott)
- **Colloidal Dynamics**
  (*Ravi Sharma* / Jan Vermant / Eric Furst)
- **Protein Adsorption**
  (*Maria Santore* / Erwin Vogler / Igal Szleifer / Kyle Vanderlick)
- **Historical Perspective**
  (Hyuk Yu)

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## COMPOSITES

Jan 13-18, 2008
Crowne Plaza
Ventura, CA
Chair: Ton Peijs
Vice Chair: Gale Holmes

- **Nanocomposites**
  (*H. Daniel Wagner* / Sanford S. Sternstein / Thomas J. Pinnavaia)
- **Dispersion of Nanofillers**
  (*Emmanuel Giannelis* / Jean-Francois Gerard / Cor Koning / Philippe Dubois)
- **Modelling of Nanocomposites**
  (*John Naim* / Bella Pukanszky / Thomas S. Gates)
- **New Nanofillers**
  (*Costas Galiotis* / Ray H. Baughman / Rodney S. Ruoff / Rod Lakes)
- **Polymers at Surfaces**
  (*Larry Drzal* / Doros N. Theodorou / Linda S. Schadler)
- **Multi-Functional Composites**
  (*Lars Berglund* / L. Catherine Brinson / Karl Schulte / Jean-Francois Feller)
- **Biobased Nanocomposites**
  (*Takashi Nishino* / Amar K. Mohanty / Hiroyuki Yano)
- **Bioinspired Composites**
  (*Richard Vaia* / Ilhan A. Aksay / Rolf Mulhaupt)
- **Inorganic Nanocomposites**
  (C. Jeffrey Brinker / Amiya K.Mukherjee)

### COMPUTATIONAL ASPECTS - BIOMOLECULAR NMR
May 18-23, 2008
Il Ciocco
Lucca (Barga), Italy
Chair: Rafael P. Bruschweiler
Vice Chair: Stephan Grzesiek

- **Perspectives on NMR in Structural and Systems Biology**
  (*Stephan Grzesiek* / Lewis Kay / Jeremy Nicholson)
- **NMR of Partially Folded, Unfolded and Misfolded Proteins**
  (Martin Blackledge / Julie Forman-Kay / Peter Wright)
- **Protein Structure and Dynamics by Solid-State NMR**
- **New Approaches in Rapid Multi-Dimensional NMR: Acquisition, Processing, Automation**
  (*Christina Redfield* / Thomas Szyperski / Daiwen Yang)
- **NMR Opportunities in Metabolomics & Metabonomics**
  (*Jeremy Nicholson* / Gerhard Wagner / David Wishart)
- **Exploring the Potential of Ultra-Fast / Ultra-Sensitive NMR**
  (Lucio Frydman)
- **Unique NMR Insights on Biomolecular Dynamics in Solution**
  (Lewis Kay / Joshua Wand)
- **Quantitative Computational Approaches to the Prediction of Protein Structure and Dynamics**
  (Valerie Daggett)
- **Biomolecular Complexes and Interactions**
  (Claudio Luchinat / Christina Redfield)

### CRANIOFACIAL MORPHOGENESIS & TISSUE REGENERATION
Feb 10-15, 2008
Il Ciocco
Lucca (Barga), Italy
Chair: Irma Thesleff
Vice Chair: Paul Trainor

- **Neural Crest / Early Events**
  (*Paul Trainor* / Anthony Graham / Laura Gammill)
- **Evo-Devo of Patterning**
  (*Kathleen Smith* / Shigeru Kuratani / Rich Schneider / Joan Richtsmeier)
- **Signalling**
  (*Irma Thesleff* / Yang Chai / David Wilkinson / Trevor Williams)
- **Morphogenesis**
  (*Yang Chai* / Antonio Baldini / Mike Dixon / Sally Moody)
- **Cleft Lip and Palate**
  (*Mike Dixon* / Karen Liu / Rulang Jiang)
- **Skeletal Development**
  (*Bjorn Olsen* / Stefan Mundlos / Bjorn Olsen)
- **Stem Cells**
  (*Paul Sharpe* / Freda Miller / Hans-Peter Howaldt)
- **Tissue Engineering**
  (*Malcolm Snead* / Samuel Stupp / Linda Griffith / Xiu-Ping Wang)

### DNA DAMAGE, MUTATION & CANCER
Mar 9-14, 2008
Ventura Beach Marriott
Ventura, CA
Chair: John B. Hays
Vice Chair: Joann B. Sweasy

- **Keynotes: How Mutations Cause Cancer / Cancer Stem Cells**
  (*Larry Loeb* / Max Wicha)
- **Genetic Landscapes of Cancer**
  (*Christoph Klein* / Tashiyatsu Taniguchi / Laura Wood / Fred Alt)
- **DNA-Repair Deficiency and Cancer Risk Epidemiology**
  (*Harvey Mohrenweiser* / Xifeng Wu / David Wilson)
- **Chemotherapy: DNA Repair and Damage-Signaling Implications**
  (*Peter Karran* / Anne Britt / Mark Kelley / Peter McHugh)
- **Lesion-Processing Pathways**
  (*Ed Loechler* / Nick Geacintov / Robert Fuchs / Barbara Hohn)
- **Events at Stalled Replication Forks**
  (*Alan Lehman* / Peter Burgers / Lajos Haracska / Agnnes Cordonnier / Kjungjae Myung)
- **DNA-Damage Toleration During Tissue Development, Growth and Aging**
  (*Laura Neidernhoffer* / Phyllis Strauss / Judy Campisi)
- **Recognition of DNA Damage**
  (*Wei Yang* / Lorena Beese / James Stivers / Jennifer Broadbelt)
- **Novel Mechanisms of Genomic Instabililty**
  (*Joann Sweasy* / Karen Vasquez / Peter Glazer / Robert Wells)

### ELECTROCHEMISTRY
**Electrochemistry For A Cleaner Environment And A Sustainable Energy Future**
Jan 6-11, 2008
Crowne Plaza
Ventura, CA
Chair: Viola I. Birss
Vice Chair: Stephen E. Creager

- **Solar Energy Conversion**
  (*Bruce Parkinson* / Moungi Bawendi / Michael Graetzel / Joop Schoonman)
- **Materials for Capacitors, Batteries, and Fuel Cells**
  (Andreas Stein)
- **From $H_2$ to Nuclear**
  (Dave Shoesmith)
- **Biological Energy Systems**
  (*Shelley Minteer* / Derek Lovley)
- **Interfacial Structures and Processes**
  (Rob Hillman / Alexei Kornyshev / Andrea Russell)
- **New Sensing Strategies**
  (*Petr Vanysek* / Art Janata)
- **High Temperature and Solid State Electrochemistry**
  (*Sossina Haile* / Stuart Adler / Clare Grey)
- **Electrocatalysis**
  (Daniel DuBois / Andy Gewirth / Umit Ozkan)
- **Open Session**
  (*Steve Creager*)

### NEW! FIBROBLAST GROWTH FACTORS IN DEVELOPMENT & DISEASE
Mar 2-7, 2008
Il Ciocco
Lucca (Barga), Italy
Chairs: Dave Fernig & Gail Martin
Vice Chair: Sabine Werner

- **Keynote Talk 1: Structure and Function of FGF Receptors**
  (Moosa Mohammadi)
- **Keynote Talk 2: The Function of FGF Signaling in Development and Disease**
  (David Ornitz)
- **FGF Function in Organogenesis**
  (*Gail Martin* / Matthew Hoffman / Tom Kornberg / Blanche Capel / Suzi Mansour / Nobu Itoh)
- **Development of the Nervous System**
  (*Ivor Mason* / Patrick Doherty / Juha Partanen / Hisashi Umemori)
- **Skeletal Biology**
  (*David Ornitz* / William Horton / Claudio Basilico / Victor Nurcombe / Irene Hung / Janet Henderson)
- **Nervous System Function and Repair**
  (*Juha Partanen* / Klaus Unsicker / Marco Riva / Claudia Grothe / Ann Logan)
- **Tumorigenesis**
  (*Victor Nurcombe* / François Radvanyi / Richard Grose / Michael Seckl / Marco Presta)
- **Homeostasis**
  (*Sabine Werner* / Alexei Kharitonenkov / Wallace McKeehan / Itaru Urakawa / Makoto Kuro-o)
- **Stem Cells, Regeneration and Tissue Repair**
  (*Janet Henderson* / Sabine Werner / Gerald de Haan / Bradley Olwin / Irma Thesleff)
- **Regulating the FGF Signal**
  (*Moosa Mohammadi* / Jeremy Turnbull / Arthur Lander)

### GENES & BEHAVIOR
Feb 24-29, 2008
Il Ciocco
Lucca (Barga), Italy
Chair: Marla Sokolowski
Vice Chair: David F. Clayton

- **Mechanistic and Evolutionary Perspectives on Genes and Behavior**
  (*Ken Kendler, David Clayton* / Gene Robinson / Nick Martin / Mark Kirkpatrick)
- **Epigenetics and Evo/Devo**
  (*Doug Emlen, Michael Meaney* / Moshe Szyf / John Ewer)
- **Trainee Data Blitz**
  (*Allen Moore*)
- **Conflict and Cooperation**
  (*Joan Strassman, Alison Bell* / Kevin Foster / Laurent Keller / Ed Kravitz)
- **Vertebrate Social Life**
  (*Darcy Kelly, Stephen Suomi* / Russ Fernald / Larry Young / Benoist Schaal / Donna Maney / David Skuse)
- **Behavior, Imaging and Genomics**
  (*Bob Hitzemann, Daisuke Yammamoto* / Martin Heisenberg / Gero Miesenbock / Seth Grant)
- **Courtship, Mating and Sexual Selection**
  (*Mariana Wolfner* / Gro Amdam / Barry Dickson / Tracey Chapman)

- **Sleep and Rhythms**
  (*Martha Merrow, Bambos Kyriacou* / Rudi Costa / Paul Shaw)
- **Language and Communication**
  (*Joel Levine* / Andy Barron / Leslie Vosshall / Bill Shafer / Constance Scharff / Simon Fisher)
- **Genes and Behavior: Unifying Principles?**
  (*Jonathan Flint, Cathy Rankin* / Ralph Greenspan)

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## GLYCOLIPID & SPHINGOLIPID BIOLOGY

Feb 17-22, 2008
Il Ciocco
Lucca (Barga), Italy
Chair: Gerrit Van Meer
Vice Chair: Lina M. Obeid

- **Sphingolipid Microdomains in Transport and Signaling**
  (*Erwin London* / Jerry Feigenson / Kai Simons / Alex Prinetti)
- **Biophysics of (Glyco)sphingolipids and Cholesterol**
  (Sandro Sonnino / Bodil Ramstedt)
- **Sphingolipids and Immunology**
  (*Hugh Willison* / Gennaro De Libero / Laura Allende / Susumu Kusunoki)
- **Storage Diseases and Diabetes**
  (*Yusuf Hannun* / Konrad Sandhoff / Fran Platt / Hans Aerts / Seng Cheng)
- **Novel Techniques; Sphingolipidomics**
  (*Al Merrill Jr.* / Akemi Suzuki / Howard Riezman / Jasna Peter-Katalinic)
- **Sphingolipid Metabolism and Transport**
  (*Yoshio Hirabayashi* / Joost Holthuis / Raman Singh / Thorsten Hornemann / Tony Futerman)
- **Sphingolipid Signaling and Autophagy**
  (*Julie Saba* / Sarah Spiegel / Patrice Codogno / Timothy Hla)
- **Sphingolipids and Cancer; Skin**
  (*Richard Kolesnick* / Amy Paller / Jim Norris / Mark Kester / Alexander Carpinteiro)
- **Mouse Models for Sphingolipid Defects/Cancer and Diet**
  (*Yasu Igarashi* / Koichi Furukawa / Ron Schnaar / Åke Nilsson)

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## GRADUATE RESEARCH SEMINAR: BIOINORGANIC CHEMISTRY

Jan 31 - Feb 3, 2008
Four Points Sheraton / Holiday Inn Express
Ventura, CA
Chair: Samuel Pazicni
Vice Chair: Faith E. Jacobsen

- **Cell Biology of Metals**
  (*Carol Fierke*)
- **Bio-Inspired Inorganic Chemistry**
  (*Patrick Farmer*)
- **Metals in Health and Medicine**
  (*Chris Orvig*)
- **Spectroscopic and Computational Insights into Metalloenzyme Structure**
  (*Michael Green*)
- **Metalloenzyme Structure, Function, and Mechanism**
  (*Judith Burstyn*)

The **Graduate Research Seminar on Bioinorganic Chemistry** is held in conjunction with the **Gordon Research Conference on Metals in Biology** (attendance at both meetings is not required).

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## ISOTOPES IN BIOLOGICAL & CHEMICAL SCIENCES

Feb 17-22, 2008
Crowne Plaza
Ventura, CA
Chair: Daniel M. Quinn
Vice Chair: John P. Richard

- **Enzyme Mechanisms From Isotope Effects**
  (*W. Wallace Cleland* / David Silverman / Ralph Pollack)
- **Isotopic Probes of Inorganic and Organometallic Reactivity**
  (*Guy Lloyd-Jones* / John Bercaw / John Groves / Roy Periana)
- **Isotopic Methods of Analysis**
  (*David Perrin* / Lingjun Li / Anil Modak)
- **Isotopic Probes of Organic Structure and Reactivity**
  (*Piotr Paneth* / Charles Perrin / Olle Mattson / Veronica Bierbaum)
- **Hydrogen Bond Structure and Function**
  (*Poul Erik Hansen* / Jan Jensen)
- **Environmental and Atmospheric Chemistry**
  (*Mark Thiemens* / Carl Brenninkmeijer / Vicki Grassian)
- **Transition States of Enzyme Reactions**
  (*Paul Fitzpatrick* / Mike Toney / Anthony Sauve)
- **Biomolecular Structure and Function: A Symposium in Honor of Maurice Kreevoy**
  (*Hans Limbach* / Judith Klinman / Jacob Schaefer / Giovanni Gadda)
- **Computational Chemistry and Isotope Effects**
  (*Vicent Moliner-Ibáñez* / Arieh Warshel / Darrin York)

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## LIGAND RECOGNITION & MOLECULAR GATING

Mar 2-7, 2008
Ventura Beach Marriott
Ventura, CA
Chair: Susan Buchanan
Vice Chair: Carola Hunte

- **Keynote Lecture: Structure and Mechanism of ABC Transporters**
  (*Susan Buchanan* / Kaspar Locher)
- **Small and Large Molecule Transport**
  (*Carola Hunte* / Mike Maguire / Mike Merrick / Jim Naismith / Amanda Stouffer / Emad Tajhorshid / Vinzenz Unger)
- **Nucleotide-Coupled Transport**
  (*Vinzenz Unger* / Poul Nissen / Heather Pinkett / Peter Tieleman)
- **Ligand-Gated Ion Channels**
  (*Rick Aldrich* / Myles Akabas / Claudio Grosman / Mark Mayer)
- **Voltage-Gated Ion Channels**
  (*Mark Mayer* / Rick Aldrich / Eduardo Perozo / Mark Sansom / Kenton Swartz / David Yue)
- **Lipid-Protein Interactions and Folding**
  (*Kenton Swartz* / Carol Deutsch / Gunnar von Heijne / Zhe Lu)
- **Ligand Recognition in G-Protein Coupled Receptors**
  (*Reinhard Grisshammer* / Hisato Jingami / Brian Kobilka / Gebhard Schertler / Roger Sunahara)
- **Channels and Receptors Assessed by NMR**
  (*Jean-Luc Popot* / Volker Dötsch / Steve Smith / Lynmarie Thompson)
- **New Methods for Structural Analysis of Membrane Proteins**
  (*Gebhard Schertler* / Filippo Mancia / Jean-Luc Popot / Chris Tate)

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## MAGNESIUM IN BIOCHEMICAL PROCESSES & MEDICINE

Mar 9-14, 2008
Crowne Plaza
Ventura, CA
Chair: William B. Weglicki
Vice Chair: Federica I. Wolf

- **Imaging the Cell Mg Homeostasis**
  (*M. Schweigel* / J. McGuigan / E. Froschauer / S. Iotti / B. Cho / K. Oka)
- **Cellular Physiology of Mg Transport**
  (*A. Fleig* / T. Guderman / L. Yue / F. van Leeuwen / A. Ryazanov)
- **Mg and Inflammatory Processes**
  (*A. Mazur* / K. Franz / J. Chmielinska / R. Rude / A. Romani)
- **Mg and the Cardio-Cerebrovascular System: From Bench to Bedside**
  (*J. Maier, R. Touyz* / P. Flatman / M. Schecter / J. Saver / D. McCarron / L. Jacobson)
- **Mg in Neuroscience: Mental Health**
  (*R. Vink* / H. Murck / R. Elin / V. Papadopol)
- **Functional and Evolutionary Aspects of Cellular Mg Transport**
  (*R. Bindels* / A. Sharenberg / R. Schweyen / J. Payandeh)
- **Mg in the Pathogenesis of the Cardio-Metabolic Syndrome**
  (*M. Barbagallo, F. Guerrero-Romero* / K. He / J. Nadler / S. Liu / J. Romero)

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## MARINE NATURAL PRODUCTS

Feb 24-29, 2008
Ventura Beach Marriott
Ventura, CA
Chair: Phillip Crews
Vice Chair: Guy T. Carter

- **Collaborative Approaches to New Discovery**
  (*Nobuhiro Fusetani* / Chris Ireland / Amy Wright / Motomosa Kobayashi)
- **New Dimensions on Inspirational Molecular Structures**
  (*Val Paul* / Sachiko Tsukamoto / Julia Kubanek / Abimael Rodriguez / Angelo Fontana)
- **Strategies for Discovery and Analysis**
  (*Ted Molinski* / Peter D.R. Moeller / Ricardo Riguera / Gabi Koenig)
- **Chemical Biology, Chemical Genetics & Biosynthetic Pathways**
  (*Eric Schmidt* / David Sherman / Bill Gerwick / Brad Moore / Joern Piel)
- **Synthesis and Medicinal Chemistry**
  (*John Pettus* / Dan Romo / Larry Overman / Melvin J. Yu / Ray Andersen / Janiine Cosy)

- **Hot Stuff From Future Luminaries**
  (*Yuzuru Shimizu* / Roger Linington / Robert Cichewicz / Coran M. H. Watanabe / Kerry McPhail / Philip Williams / Taro Amagata)
- **Tapping Microbial Diversity**
  (*Marcel Jaspars* / Bill Fenical / Jeff Wright / Alan T. Bull / Peter Proksch / Weiming Zhu)
- **Developing Therapeutics & Molecular Probes**
  (*Henonjoung Kang* / Fred Valeriote / Sue Mooberry / Ron Quinn)

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**NEW! MECHANICAL SYSTEMS IN THE QUANTUM REGIME**
Feb 17-22, 2008
Four Points Sheraton / Holiday Inn Express
Ventura, CA
Chairs: Jack G. E. Harris & Andrew Cleland
Vice Chairs: Keith C. Schwab & David McClelland

- **The Standard Quantum Limit and Beyond, Part 1**
  (*Steven Girvin* / Keith Schwab / David McClelland)
- **Cooling and Control**
  (*Howard Wiseman* / Antoine Heidmann / Konrad Lehnert / Markus Aspelmeyer)
- **The Standard Quantum Limit and Beyond, Part 2**
  (*Gerard Milburn* / Yanbei Chan / Roman Schnabel)
- **Entanglement & Quantum Information in Mechanical Systems**
  (*Miles Blencowe* / Paolo Tombesi / Dirk Bouwmeester / Lin Tian)
- **Advances in Materials and Fabrication**
  (*Michael Roukes* / Melissa Hines / Kerry Vahala)
- **Mechanics of the Quantum Vacuum**
  (*Steve Lamoreaux* / Federico Capasso / Astrid Lambrecht / Marlon Scully)
- **Mechanical Approaches to Nonclassical States**
  (*Ping Koy Lam* / Nergis Mavalvala / Andrew Armour)
- **Mechanical Coupling to Quantum Systems**
  (*John Sidles* / Leonid Levitov / Daniel Rugar / Roberto Onofrio)
- **Frontiers of Mechanical Quantum Systems**
  (*Anthony Leggett* / Alex Zettl / Kenton Brown)

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**METALS IN BIOLOGY**
Jan 27 - Feb 1, 2008
Four Points Sheraton / Holiday Inn Express
Ventura, CA
Chair: Julie A. Kovacs
Vice Chair: Peter M. Kroneck

- **Keynote Talk: Mechanisms of Energy Conversion in Biology and Chemistry**
  (*Harry Gray* / Daniel Nocera)
- **Thermophilic Metalloenzymes**
  (*Peter Kroneck* / Fred Hagen / Dianne Newman / Arnulf Kletzin)
- **Sulfur's Influence on Metalloenzyme Function I: Clusters**
  (*Steve Ragsdale* / Paul Lindahl / Richard Holm)
- **Sulfur's Influence on Metalloenzyme Function II**
  (*Marty Kirk* / Charles Riordan / Jason Shearer / Sean Elliott / Michael Maroney)
- **O-O Bond Cleavage and Formation I**
  (*Bill Tolman* / John Groves / Elodie Anxolabehere-Mallart)
- **O-O Bond Cleavage and Formation II**
  (*Simon de Vries* / Shelagh Ferguson-Miller / Ken Karlin / Edward Solomon)
- **Oxidative Stress and Reactive Oxygen Species**
  (*Joan Valentine* / Diane Cabelli / Chris Chang / Katherine Franz)
- **Bioinspired Catalysis**
  (*Jonas Peters* / Thomas Ward / T.D.P. Stack / Larry Que)
- **Joint Session with Graduate Research Seminar / Keynote Talk**
  (*Steve Lippard* / Thomas V. O'Halloran)

The **Gordon Research Conference on Metals in Biology** is held in conjunction with the **Graduate Research Seminar on Bioinorganic Chemistry** (attendance at both meetings is not required).

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**MOLECULAR EVOLUTION**
Feb 3-8, 2008
Crowne Plaza
Ventura, CA
Chair: Billie J. Swalla
Vice Chair: David Rand

- **Exploring Adaptive Landscapes**
  (*Ben Kerr* / Tony Dean / Dan Weinrich)
- **Evolvability**
  (*Günter Wagner* / Lilach Hadany / Suzannah Rutherford / Susan Rosenberg)
- **Phylogenomics**
  (*Laura Katz* / Monica Medina / Jennifer Hughes)
- **Molecular Evolution of Body Axes**
  (*Mike Levine* / Elaine Seaver / Mark Martindale / John Gerhart)
- **Positive and Negative Selection on Noncoding DNA**
  (*Peter Andolfatto* / Manolis Dermitzakis / Ed Rubin)
- **Measuring Evolutionary Timescales**
  (*Bret Payseur* / Sarah Tishkoff / Asher Cutter / Joanna Mountain)
- **Molecular Basis of Heart Evolution**
  (*Doug Crawford* / Brad Davidson / Jose Xavier-Neto)
- **Computational and Statistical Advances**
  (*Sudhir Kumar* / David Haussler / Carlos Bustamante / Lindell Bromham)
- **Microevolution of Development**
  (*Norman Johnson* / Eric Haag / Hope Hollocher)

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**MOLECULAR MECHANISMS IN LYMPHATIC FUNCTION & DISEASE**
Mar 2-7, 2008
Four Points Sheraton / Holiday Inn Express
Ventura, CA
Chair: Geert Schmid-Schonbein
Vice Chair: Michael J. Detmar

- **Growth Factor Mechanisms and Stem Cells in Lymphangiogenesis**
  (*Guillermo Oliver* / Kari Alitalo / Brant Weinstein / Michael Detmar / Peter Carmeliet)
- **Lymphatic Vasculature in Immunity and Inflammation**
  (*Dieter Maurer* / Uli van Andrian / Gwendalyn Randolph / David Jackson / Dontscho Kerjaschki)
- **Lymphatic Vessel Morphogenesis and Maturation**
  (*David Jackson* / Taija Mäkinen / Anne Eichmann / Toshio Ohhashi)
- **Signal Transduction in Lymphatic Endothelium and Smooth Muscle**
  (*Taija Mäkinen* / Lena Claesson-Welsh / Elisabetta Dejana / Hellmut G. Augustin / Donald McDonald)
- **Transcriptional Regulation of Lymphangiogenesis**
  (*Brant Weinstein* / Guillermo Oliver / Peter Koopman / Tatiana Petrova / Dieter Maurer)
- **Molecular Control of Lymph Transport Activity and Tissue Engineering**
  (*Peter Carmeliet* / Melody Swartz / David Zawieja / David Bates)
- **Lymphatic Metastasis**
  (*Kari Alitalo* / Michaela Skobe / Marc Achen / Rakesh Jain / Judith Varner)
- **Genetics and Treatment of Lymphatic Dysorders**
  (*David Zawieja* / Peter Mortimer / Tuomas Tammela / Stanley Rockson / Miikka Vikkula)
- **Pathological Lymphangiogenesis and Lipid Transport**
  (*Michaela Skobe* / Gou Young Koh / Bronek Pytowski / Young Kwon Hong)

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**MYELIN**
May 4-9, 2008
Il Ciocco
Lucca (Barga), Italy
Chair: Peter J. Brophy
Vice Chair: Wendy B. Macklin

- **Keynote Talk: Myelination and Demyelination - Progress, and Major Unsolved Questions**
  (David Colman / Bruce Trapp / Boris Zalc)
- **Junctional Complexes, Axo-Glial Interactions and Assembly of the Node of Ranvier**
  (*Steven Scherer, Ori Peles*)
- **Peripheral Neuropathies: Lessons for Schwann Cell Biology**
  (*Kristjan Jessen, Dies Meijer*)
- **Signaling and Transcriptional Regulation in Myelinating Glia**
  (*Nancy Ratner, Jim Salzer*)
- **White Matter Diseases: Lessons for MS?**
  (*David Rowitch, Charles ffrench-Constant*)
- **Repair and Regeneration In Vivo**
  (*Marie Filbin, Anne Baron-Van Evercooren*)
- **Extracellular Signaling and Myelination in CNS and PNS**
  (*Robert Miller, Klaus-Armin Nave*)
- **Glial Cell Death and Axonal Pathology**
  (*Larry Wrabetz, Julia Edgar*)
- **Animal Models of Demyelination: Have We Learned Anything Useful?**
  (*Robin Franklin, Richard Reynolds*)

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**NEW! NEW ANTIBACTERIAL DISCOVERY & DEVELOPMENT**
Mar 9-14, 2008
Il Ciocco
Lucca (Barga), Italy
Chair: Robert E.W. Hancock
Vice Chair: Jutta Heim

- **The Picture Today and Tomorrow - Keynote Addresses**
  (*Trevor Trust* / Julian Davies / Karen Bush)
- **Conventional Targets**
  (*Lynn Silver* / Prabhavathi Fernandes / Roy Kishony / Hans Georg Sahl / Ann Eakin / Roger C. Levesque)
- **Screening Strategies and Hit Generation**
  (*Ken Stover* / Jay Hinton / Dieter Habich / Jennifer Leeds)
- **Alternative Antibacterial Approaches**
  (James Mond / John North / Vincent Fischetti / Alan Bocking)
- **Pre-Clinical and Clinical Considerations**
  (*David Payne* / John Rex / Keith Rodvold / Robert Munford)
- **Gram Negative Active Drugs**
  (*Laura Piddock* / Matthew E. Falagas / Tim Falla / Dirk Buman / Natalie Strynadka)
- **Novel Targets and Overcoming Resistance**
  (*Jared Silverman* / Patricia Bradford / Sheo Singh / Satoshi Murakami / Eric Brown)
- **Selected Topics & Late Breakers**
  (*Patrice Courvalin*)
- **Recent Experience with Clinical Trials**
  (Jutta Heim / Bruce Montgomery)
- **Towards More Efficient Antibacterial Development**
  (*Keith Poole* / Jacques Schrenzel / Rod Hubbard / Rudolf Then)

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**ORGANIC STRUCTURES & PROPERTIES**
**Molecular Design & Supramolecular Assemblies**
Apr 27 - May 2, 2008
Il Ciocco
Lucca (Barga), Italy
Chairs: Mireille Blanchard-Desce & Joanna Aizenberg
Vice Chair: Vincent M. Rotello

- **From "Solid" to "Fuzzy" Organization - Challenges and Scope of Self-Organization I: Crystal Engineering**
  (G. Desiraju / F. Grepioni / K. Rissanen)
- **From "Solid" to "Fuzzy" Organization - Challenges and Scope of Self-Organization II: From Supramolecular Organization in the Solid State to Self-Assembly**
  (W. Hosseini / R. Resnati / G. Decher)
- **New Frontiers in Modular Control of Properties (Ionic Liquids / Modified Quantum Dots)**
  (F. Stellacci / R. Rodgers)
- **Supramolecular Chemistry and Dynamics**
  (J.-M. Lehn / J. Rebek / V. Balzani)
- **Molecular Nanomachines and Dynamic Structures**
  (C. Barrett / B.L. Feringa)
- **Molecular/Supramolecular Photonics: Functional Molecules to Functional Materials**
  (S.R. Marder / L. De Cola / F. Würthner)
- **Biomaterials: Functional Architectures From Molecular Chemistry**
  (Z. Guan / K. Johnsson)
- **Bio(inspired) Materials**
  (L. Addadi / L. Estroff / T. Douglas)
- **Architecture-Structure-Property Control in Polymers/Dendrimers**
  (T. Swager / A.M. Caminade)

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**ORIGIN OF LIFE**
Jan 20-25, 2008
Crowne Plaza
Ventura, CA
Chair: Robert M. Hazen
Vice Chair: George E. Fox

- **From Scenarios to Schemas: Robust Models for Life's Origins**
  (Harold Morowitz / John Baross)
- **Real World Geochemical Complexity: Interfaces, Gradients and Cycles**
  (Victoria Orphan / Kevin Zahnle / Ariel Anbar / Michael Russell)
- **Alternative Planetary Environments for Life**
  (Dirk Schulze-Makuch / Darlene Lim / Athena Coustensis / Steve Benner)
- **Roots of, and Roots to, Metabolism**
  (George Cody / Nicolas Platts / Shelley Copley / Eric Smith)
- **Metabolism First: An Abundance of Worlds**
  (Robert Shapiro / Eörs Szathmáry / Arthur Weber / Irene Chen)
- **The Legacy of Stanley Miller: Heterotrophic Origins**
  (Jeffrey Bada / Antonio Lazcano / H. James Cleaves / Peter Nielsen)
- **Progress Towards Synthesizing an Artificial Cell**
  (Jack Szostak)
- **The Origins of Biochemical Homochirality**
  (Donna Blackmond)
- **The Case for the RNA World**
  (John Sutherland / Harry Moller / Reza Ghadiri / Ram Krishnamurthy)
- **Reconciling the Metabolism First versus RNA First Debate**
  (Nigel Goldenfeld / Gunter von Kiedrowski)

**NEW! GRADUATE RESEARCH SEMINAR: ORIGIN OF LIFE**
Jan 19-20, 2008
Crowne Plaza
Ventura, CA
Chairs: Luis Delaye & Nicole R. Posth

The **Graduate Research Seminar on Origin of Life** is a two-day Gordon Conference-style meeting exclusively for graduate students and postdoctoral fellows. Speakers will be chosen from among the attendees. The **Gordon Research Conference on Origin of Life** will take place at the same location, immediately following the Seminar.

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**OXYGEN RADICALS**
Feb 3-8, 2008
Ventura Beach Marriott
Ventura, CA
Chairs: Stanley L. Hazen & Kevin Moore
Vice Chairs: Garry Buettner & Anthony J. Kettle

- **Superoxide Dismutase (SOD)**
  (*John Keaney* / Joe Beckman / Serpil Erzurum)
- **Oxidative Stress, Inflammation and Cardiovascular System**
  (*Serpil Erzurum* / Cecelia Giulivi / John Keaney / Neil Granger / Clay Semenkovich)
- **Oxidized Lipids and Disease Mechanisms**
  (*Valerian Kagan* / Eugene Podrez / Valerie O'Donnell)
- **NO / Nitrite Biochemistry and Disease**
  (*Victor Darley-Usmar* / Mark Gladwin / Andrew Gow / Jon Lundberg / Rakesh Patel)
- **Iron Proteins and Oxidative Stress**
  (*Valerie O'Donnell* / Raman Kalyanaraman / Paul Fox)
- **Chemistry of Thiols and Thiol Signaling**
  (*Raman Kalyanaraman* / Neil Hogg / Richard Cohen / Michael Murphy / Phillip Moore)
- **Diabetes and Oxidative Stress**
  (*Clay Semenkovich* / Michael Brownlee / David Stern)
- **Mitochondria and Free Radical Generation**
  (*Cecelia Giulivi* / Victor Darley-Usmar / Robert Balaban / Valerian Kagan / Shruti Shiva)
- **Oxidative Chemistry and Disease Processes**
  (*Joe Beckman* / Joe Loscalzo)

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**PEPTIDES, CHEMISTRY & BIOLOGY OF**
Feb 17-22, 2008
Ventura Beach Marriott
Ventura, CA
Chairs: Carrie Haskell-Luevano & Kit S. Lam
Vice Chairs: Samuel H. Gellman & Mark R Spaller

- **Peptide/Protein Design Strategies**
  (Henry Mosberg / George Barany / Jerry "Ryan" Holder / Mike Pennington)
- **Folding and Dynamics**
  (*Gouri Jas* / Krzysztof Kuczera / Peter Steinbach / Charles Brooks III)
- **Ligand-Protein Interactions**
  (Tomi Sawyer / Maria Bednarek / Dennis Dougherty)
- **Infectious Diseases**
  (*Bob Hodges* / Alanna Schepartz / Jean Chmielewski / Bob Hodges)
- **New Chemistry Approaches in Peptide Science**
  (*Fernando Albreico* / Scott Miller / Richard Houghten / Fernando Albreico / Jon Ellman)
- **Material Science/Nanotechnology**
  (*Hiroshi Matsui* / Morley Stone / Hiroshi Matsui / Ehud Gazit)
- **Chemical Biology & Molecular Imaging**
  (Tom Kodadek / Xiaoyuan "Shawn" Chen / Nathanael Gray / Yvonne Angell)

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**PHOTOACOUSTIC & PHOTOTHERMAL PHENOMENA**
**Photoinduced Processes And Applications**
Feb 10-15, 2008
Crowne Plaza
Ventura, CA
Chair: Masahide Terazima
Vice Chair: Vitalyi Gusev

- **Photon-Materials Interaction and Spectroscopy**
  (*C.D. Tran* / Rolf Hemberg / S. Bialkowski / G. Diebold)

- **Nanoscale and Quantum Phenomena**
  (David G. Cahill / F. Vallee / Arun Majumdar)
- **Ultrafast Phenomena**
  (*K. Katayama* / M.A. El-Sayed / Masashi Yamaguchi)
- **Imaging and Microscopy**
  (Alfred Vogel)
- **Chemical, Biological, and Medical Applications**
  (Vladimir Zharov / A. Hammiche)
- **Laser-Based Diagnostics**
  (*H. Talaat* / A.A. Karabutov / Gilles Tessier)
- **Nondestructive Evaluation**
  (A. Mandelis / Claire Prada)
- **Materials Processing**
  (Ingolf Hertel / P. Hess)
- **Mechanisms of Photon-Materials Interaction and Removal**
  (Leonid Zhigilei / Akos Veres)

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## PHOTOIONS, PHOTOIONIZATION & PHOTODETACHMENT

Jan 27 - Feb 1, 2008
Il Ciocco
Lucca (Barga), Italy
Chair: Klaus Müller-Dethlefs
Vice Chair: Albert Stolow

- **Photodetachment**
  (*Carl Lineberger* / Dan Neumark / Bob Continetti)
- **Electron Correlation in Scattering and Photoionization**
  (*Uwe Becker* / Lorenz Cederbaum / Georg Prümper / Stefano Stranges / George King)
- **Ultrafast Time-Resolved Photoionization Spectroscopy**
  (*John Dyke* / Masaaki Fujii / Valérie Blanchet)
- **ZEKE Rydberg Probes of Molecules and Clusters**
  (*Yuxiang Mo* / Cheuk-Yiu Ng / Myung Soo Kim / Wen-Bih Tzeng)
- **Cold Rydberg Plasmas and Coulomb Crystals**
  (*Chris Greene* / Tom Gallagher / Pierre Pillet)
- **Photoionization**
  (*Erwin Poliakoff* / Piero de Cleva / Eric Charron / Franco Vecchiocattivi / J. Vince Ortiz)
- **Towards Attosecond Dynamics**
  (*Thomas Baumert* / Mischa Ivanov / Margaret Murnane)
- **Novel Methods for Molecular Dynamics**
  (*K. Ueda* / Reinhard Dörner / Bill McCurdy)
- **Hot Topics**
  (*Mark Johnson*)
- **Biological Molecules and Radiation Damage**
  (*Ed Grant* / Andrew Bass / Franco Gianturco)
- **Keynote Address: A Lifetime of Rydberg States**
  (Christian Jungen)

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## PHOTOSENSORY RECEPTORS & SIGNAL TRANSDUCTION

Jan 27 - Feb 1, 2008
Crowne Plaza
Ventura, CA
Chair: Klaas J. Hellingwerf
Vice Chair: Kevin H. Gardner

- **Structure and Mechanism of Signal Generation in BLUF Domains**
  (*Carl Bauer*)
- **From Structure to Signal-Transduction Chain in the Phytochrome Family**
  (*Eberhard Schaefer*)
- **New Techniques for the Study of Photosensory Signal Transduction**
  (*Pill-Soon Song*)
- **From Structure to Function in Visual Rhodopsins**
  (*Kris Palczewski, Bob Birge*)
- **Microbial Rhodopsins: Diversity, Structure, and Mechanism of Signal-Generation and Transfer**
  (*John Spudich*)
- **The Mechanism of Signal Transfer Mediated by LOV Domains**
  (*Peter Hegemann*)
- **Blue-Light Photoreception**
  (*Michael Cusanovich*)
- **The Mechanism of Signal Generation in Cryptochromes**
  (*Aziz Sancar*)
- **On the Application of Light-Sensing Proteins**
  (*Georg Nagel*)

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## PINEAL CELL BIOLOGY

### Mechanisms Of Circadian Rhythmicity And Melatonin Action

Apr 20-25, 2008
Il Ciocco
Lucca (Barga), Italy
Chair: Jörg H. Stehle
Vice Chair: David R. Weaver

- **Regulation of Pineal Melatonin Synthesis - New Twists in an Old Story**
  (*Helena Illnerova* / Steven Coon / Valérie Simonneaux / Anthony Ho)
- **Melatonin Receptors - What Are They Good For?**
  (*David Weaver* / Ralf Jockers / Jean Boutin / Benoît Malpaux / Jonathan Johnston)
- **Management of Time in Human Chronobiology**
  (*Alfred Lewy* / Till Roenneberg / Debra Skene / Steven Lockley / Shantha Rajaratnam)
- **Retina and Melatonin - Seeing the Clock?**
  (*Michael Iuvone* / Gianluca Tosini / Russell Foster / Ignacio Provencio)
- **Rhythms in the Periphery - The Role of Melatonin**
  (*Michael Menaker* / Andries Kalsbeek / David Hazlerigg / Sandrine Dupré)
- **Pineal Regulators During Evolution, through Life-Span, with Season, Day-by-Day**
  (*Horst-Werner Korf* / Elise Cau / Yoav Gothilf / Dick Swaab)
- **Linking Melatonin and Clocks with Disease and the Immune System**
  (*George Brainard* / David Blask / Marina Antoch / Eus van Someren)
- **The Role of the Pineal in Clocking Seasonal Adaptation**
  (*David Kennaway* / Annika Herwig / Brian Barnes / Gerald Lincoln)
- **Invited Poster Talks from Submitted Abstracts**
  (*Carla Green, Andrew Loudon*)
- **Keynote Talk I: The Global Nature of the Daily Rhythms in Rodent Pineal Gene Expression**
  (*Elizabeth Maywood* / David C. Klein)
- **Keynote Talk II: Impact of Melatonin on Human Health**
  (*Martin Zatz* / Josephine Arendt)

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## PLASMINOGEN ACTIVATION & EXTRACELLULAR PROTEOLYSIS

Feb 10-15, 2008
Four Points Sheraton / Holiday Inn Express
Ventura, CA
Chair: Toni Antalis
Vice Chairs: Thomas H. Bugge & Niels Behrendt

- **Receptors in Thrombosis and Fibrinolysis**
  (*Ed Plow* / Shaun Coughlin / Lindsay Miles / Michael Ploug)
- **Inflammation, Pathogenesis and Host Defense**
  (*William Goldman* / Jay Degen / Wyndham Lathem / Stephen Smiley)
- **Proteolytic Pathways**
  (*Sidney Strickland* / Katherine Hajjar / Vincent Ellis / Jeffrey Smith)
- **Dysregulated Proteolysis**
  (*Victoria Ploplis* / Roman Szabo / Daniel Kirchhofer / Francesco Blasi)
- **Proteolysis in Tumor Biology**
  (*Steven Gonias* / Harold Chapman / Sharon Stack / Peter Friedl)
- **Neurobiology and Neurological Diseases**
  (*Stella Tsirka* / Katerina Akassoglou / Dan Lawrence / Wendy Campana / Sidney Strickland)
- **Late Breaking Hot Topics from Abstracts**
  (*Thomas Bugge, Niels Behrendt*)
- **Atherosclerosis and Cardiovascular Disease**
  (*Dudley Strickland* / Qingyu Wu / David Ginsburg / Dudley Strickland)
- **Protease Engineering**
  (Ed Madison / Thomas Bugge)

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## PROLACTIN & GROWTH HORMONE FAMILY

Feb 10-15, 2008
Ventura Beach Marriott
Ventura, CA
Chair: Hallgeir Rui
Vice Chair: Vincent Goffin

- **Transcriptional Control of PRL and GH Genes**
  (*Hallgeir Rui* / Arthur Gutierrez-Hartmann / Nancy Cooke)
- **PRL and GH Pathway Mutations and Polymorphisms**
  (*Stephen Liebhaber* / Anders Juul / Ron Rosenfeld / Asta Försti / Philippe Touraine)
- **PRL & GH Intracellular Signaling**
  (*Linda Schuler* / Christine Carter-Su / Charles Streuli / Ted Elsasser)

- **Clinical and Pathological Aspects of PRL and GH**
  (*Charles Clevenger* / Michael O. Thorner / A.J. Van der Lely / Ross Clark / Ken Ho)
- **Stem Cells in GH and PRL Target Organs**
  (*Kay-Uwe Wagner* / Gabriela Dontu / Gil Smith / Michael Waters)
- **PRL/GH Target Organs**
  (*Geula Gibori* / Nadine Binart / Ralf Paus / Peter Lobie / Michael Freemark)
- **PRL and GH-Related Ligands**
  (*Carmen Clapp* / Joseph Martial / Denise Hilfiker-Kleiner / Richard Ross)
- **Pituitary and CNS**
  (*Julian Davis* / Dave Grattan / Robert Bridges / Sam Weiss / Shlomo Melmed)
- **Caveolins, PRL and GH in Mammary Development and Tumorigenesis**
  (*Vincent Goffin* / Michael Lisanti)

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## PROTEIN COFACTORS, RADICALS AND QUINONES

Jan 20-25, 2008
Four Points Sheraton / Holiday Inn Express
Ventura, CA
Chair: Joan B. Broderick
Vice Chair: Britt-Marie Sjoberg

- **Radical Mechanisms I**
  (Wolfgang Bückel / J. Martin Bollinger)
- **$B_{12}$ and Radical SAM Enzymes**
  (*Joseph Jarrett* / Catherine Drennan / Neil Marsh / Ruma Banerjee / Peter Roach)
- **Electron and Proton Transfer**
  (JoAnne Stubbe / Michael Sutcliffe)
- **Radical Mechanisms II**
  (Justine Roth / George Reed)
- **Cross-Linked Amino Acid Cofactors**
  (Robert Gennis / Brian Fox)
- **Complex Redox Cofactors: Mechanism**
  (*Sean Elliott* / Lance Seefeldt / Fraser Armstrong / Gary Brudvig)
- **Complex Redox Cofactors: Biosynthesis**
  (*John Peters* / Luis Rubio / Bärbel Freidrich)
- **Quinone Cofactors: Biogenesis and Mechanism**
  (Judith Klinman / Victor Davidson / Lawrence Sayre / Cecilia Tommos)
- **Chemistry and Biology of Ribonucleotide Reductases**
  (Britt-Marie Sjöberg)

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## PROTEIN FOLDING DYNAMICS

Jan 6-11, 2008
Four Points Sheraton / Holiday Inn Express
Ventura, CA
Chair: Charles L. Brooks
Vice Chair: Susan Marqusee

- **Keynote Lecture I: Unified Theory of Protein Folding, Experimental Perspective**
  (*Peter Wolynes* / S. Walter Englander)
- **Keynote Lecture II: New Frontiers, Where Shall We Head?**
  (*Peter Wolynes* / Dave Thirumalai)
- **Probing Folding and Misfolding Pathways**
  (*Valerie Daggett* / Jana Khandoghin / Bill Balch / Joan Shea)
- **Fast Folding Events**
  (*William A. Eaton* / Victor Munoz / Peter Hamm / Ken Dill)
- **Exploring Folding Landscapes and Mechanisms I**
  (*Mikael Oliveberg* / Jane Clark / Bob Matthews / Cecelia Clementi)
- **Exploring Folding Landscapes and Mechanisms II**
  (Sheena Radford / Margaret Cheung)
- **Keynote Lecture III: New Challenges and Horizons for Protein Folding Experiment and Theory**
  (*Vijay Pande* / Alan Fersht)
- **Single Molecule Folding Studies**
  (*Jose Onuchic* / Matthias Reif / Sophie Jackson / Carlos Bustamante / Ben Schuler / Julio Fernandez)
- **Membrane Mediated Folding Dynamics**
  (*Angel Garcia* / Feng Gai / Wonpil Im / Mei Hong)
- **Fluctuations and Conformational Ensembles**
  (*J. Winkler* / Vince Hilser / Bertrand Garcia Moreno / Lynne Regan)
- **Chaperones and Co-Translational Folding**
  (*Silvia Cavagnero* / Elke Deuerling / Adrian Elcock / Ulrich Hartl)

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## RADIATION ONCOLOGY
### Understanding The DNA Damage Response To Optimize Radiation Therapy

Jan 27 - Feb 1, 2008
Ventura Beach Marriott
Ventura, CA
Chair: Simon N. Powell
Vice Chair: William F. Morgan

- **Keynotes: Harnessing Biology to Optimize Radiation Therapy**
  (J. Martin Brown / Michael Kastan)
- **Increasing the Effects of DNA Damage in Tumors by Chromatin Modification**
  (*Andre Nussensweig* / Junjie Chen / Gary Kao)
- **Modification of DNA Damage Checkpoints in Tumors and Normal Cells**
  (*Helen Piwnica-Worms* / David Cortez / Jiri Bartek)
- **Adaptation From Checkpoints**
  (*Jim Haber* / Jiri Lukas / Marco Foiani)
- **Stalled Replication, Fork Cleavage, Replication Restart**
  (*Alan Lehmann* / Wolf Heyer / Bing Hui Shen)
- **Homologous Recombination Defects in Tumor Cells**
  (Alan Ashworth / Alan D'Andrea / Thomas Helleday)
- **Competition Between DNA DSB Repair Pathways**
  (Rodney Rothstein / Jac Nickoloff / Maria Jasin)
- **Effects of Hypoxia on DNA Repair**
  (*Amato Giaccia* / Peter Glazer / Robert Bristow / Ester Hammond)
- **Genomic Approaches to Studying Variations in Radiation Response**
  (*Janet Hall* / Arnold Levine / Howard Macleod)

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## SENSORY TRANSDUCTION IN MICROORGANISMS

Jan 13-18, 2008
Ventura Beach Marriott
Ventura, CA
Chair: Ann M. Stock
Vice Chair: Ann H. West

- **Receptor Amplification and Adaptation**
  (*Bob Bourret* / Brian Crane / George Ordal / Jeffry Stock / Sriram Subramaniam)
- **Bacterial Chemotaxis Mechanisms and Models**
  (*Michael Eisenbach* / Howard Berg / Frederick Dahlquist / Ikuro Kawagishi / Victor Sourjik / Yuhai Tu / Ned Wingreen / Igor Zhulin)
- **Receptor Sensing and Signaling**
  (*Gerald Hazelbauer* / Joseph Falke / Karen Ottemann / John S. Parkinson / John Spudich / Barry Taylor)
- **Molecular Mechanisms of Directed Movement**
  (*Alan Kimmel* / Judith Armitage / Rick Firtel / John Kirby / Arash Komeili / William Loomis / Liz Sockett / Zhaomin Yang)
- **Intracellular Signaling**
  (*Alan Wolfe* / Katherine Borkovich / Caroline Harwood / James Hoch / Lotte Søgaard-Andersen)
- **His-Asp Phosphorelay Signaling**
  (*Philip Matsumura* / Richard Calderone / Jan Fassler / Michael Laub / Kathleen Ryan / Kaz Shiozaki)
- **Motility and Localization**
  (*Wenyuan Shi* / Guenther Gerisch / Tâm Mignot / Peter Satir / David Zusman)
- **Motility and Structural Basis of Movement**
  (*Rüdiger Schmitt* / Shin-Ichi Aizawa / Nyles Charon / Michio Homma / Kelly Hughes / Keiichi Namba)
- **Pathogenesis and Virulence Mechanisms**
  (*Linda Kenney* / Everett P. Greenberg / Fred Hughson / Linda McCarter / Fitnat Yildiz)

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## SPIROCHETES, BIOLOGY OF

Jan 20-25, 2008
Ventura Beach Marriott
Ventura, CA
Chair: Sven A. Bergstrom
Vice Chair: Richard P. Ellen

- **Structure-Function Biology**
  (*Ben Adler* / Jaques Izard / Justin Radolf / Ira Schwarz / David Hampson)
- **Biology Related to Risk for Infection**
  (*Richard Zeurner* / Sarah Randolph / Joseph Vinetz / Jean-Francois Trapé / Jennifer C. Miller)
- **Advances in Genomes and Genetics and Past Chair Forum**
  (*Sherwood Casjens* / Patricia Rosa / Floyd Dewhirst / Nyles Charon / Alan G. Barbour / Steve Norris / Sheila Lukehart)
- **Spirochetal Transport, Environmental Signals, and Metabolism**
  (*Jared Leadbetter* / Frank Gherardini / M.A. Motaleb / Helene Louvel / Janakiram Seshu / Juan Anguita)
- **Invasion and Evasion Strategies of Spirochetal Pathogens**
  (*Chris Fenno* / Erol Fikrig / Kazuyuki Ishihara / Caroline Cameron / Jorge Benach)

- **Spirochete Biology & Diversity**
  (*Anette Moter* / Tom Schwan / Cathrine Brissette / Allen C. Steere / Betty Guo / Jay Carrol)
- **Interaction with Host Cells and Immunopathology**
  (*Linda Bockensted* / Mario Philipp / John Leong / Ruth Montgomery / Janis Weis)
- **Regulation of Replication and Gene Expression in Spirochetes**
  (*Brian Stevenson* / Jeffrey Miller / Lorenzo Giacani / Felipe Cabello / George Chaconas / David Haake)
- **Late Breaking Session**
  (*Jenifer Coburn, Kit Tilly*)

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**NEW! THIOL-BASED REDOX REGULATION & SIGNALING**
May 25-30, 2008
Il Ciocco
Lucca (Barga), Italy
Chair: Ruma Banerjee
Vice Chair: Roberto Sitia

- **Redox Signaling**
  (*Ruma Banerjee* / Vadim Gladyshev / Art Horowich)
- **Disulfide Bond Formation and Isomerization**
  (*Jim Bardwell* / Chris Kaiser / Debbie Fass / Kenji Inaba / Ineke Braakman)
- **Redox-Based Intra- and Extra-Cellular Communication**
  (*Arne Holmgren* / Dean Jones / Anna Rubartelli / Jonathan Kipnis)
- **Peroxide Generation and Clearance**
  (*Leslie Poole* / Peter Chumakov / Chris Chang)
- **Redox Sensing**
  (*Colin Thorpe* / John Helman / Stuart Lipton)
- **Mitochondrial Redox Regulation and Disease**
  (*Jon Beckwith* / Carla Koehler / Michael Murphy / Marco Giorgio / Kostas Tokatlidis)
- **Thiol Modificatios and Regulation**
  (*Michel Toledano* / Harry Ischiropoulos / Stephane Lemaire / Phil Hogg)
- **Regulation and Targeting of Sulfur Metabolism**
  (*Ursula Jakob* / Katja Becker / Peggy Baudouin-Cornu)
- **Emerging Redox Technologies**
  (*Roberto Sitia* / Ken Tew / Jim Wells)

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**NEW! ULTRAFAST PHENOMENA IN COOPERATIVE SYSTEMS**
Feb 3-8, 2008
Il Ciocco
Lucca (Barga), Italy
Chairs: Antoinette J. Taylor & Andrea Cavalleri
Vice Chair: Tony F. Heinz

- **Photoinduced Phase Transitions I**
  (Elbert Chia)
- **Photoinduced Phase Transitions II**
- **Quasiparticle Dynamics in Correlated Solids I**
  (*Antoinette Taylor* / Jure Demsar)
- **Quasiparticle Dynamics in Correlated Solids II**
  (*Richard Averitt* / Stuart Trugman)
- **Photoinduced Metal-Insulator Transitions**
  (*Andrea Cavalleri*)
- **Exciton Dynamics**
  (Tony Heinz)
- **Ultrafast Magnetism**
  (Paul Van Loosdrecht)
- **Spin Manipulation**
- **Coherent Dynamics**

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**VIRAL VECTORS FOR GENE THERAPY, THE SCIENCE OF**
Mar 2-7, 2008
Crowne Plaza
Ventura, CA
Chair: Paul D. Robbins
Vice Chair: Luigi Naldini

- **Immune Response to Viral Vectors**
  (*Paul Robbins* / Kathy High)
- **Biodistribution and Targeting**
  (*John Engelhardt* / Jude Samulski / Renata Pasqualini / Wadih Arap / Richard Vile / David Schaffer)
- **Viral Entry and Nuclear Translocation**
  (*Jude Samulski* / John Engelhardt / Arun Srivastava / Mark Kay)
- **Host Cell Response to Viral Infection**
  (*Joseph Glorioso* / Karen Mossman / Erik Falck-Pedersen / Paola Grandi)
- **Innate Immune Response to Viral Infection**
  (*James Wilson* / Daniel Muruve / Glen Nemerow / Yiping Yang)
- **Adaptive Immune Response to Viral Infection**
  (*Luigi Naldini* / Andrea Amalfitano / James Wilson / Luca Guidotti)
- **Approaches to Blocking the Immune Response to Viral Infection**
  (*Malcolm Brenner* / Luigi Naldini / Maria Grazia Roncarolo / Roland Herzog)
- **Suppression of the Immune Response by Gene Transfer**
  (*Maria Grazia Roncarolo* / Paul Robbins / David Scott / Garrison Fathman)
- **Stimulation of the Immune Response by Gene Transfer**
  (*Garrison Fathman* / Carl June / Glenn Dranoff / Malcolm Brenner / Marjorie Robert-Guroff)

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## POSITIONS OPEN

### ASSISTANT and/or ASSOCIATE PROFESSOR of HUMAN GENETICS

The Department of Human Genetics at the University of Utah School of Medicine is continuing a new major expansion, recruiting three new investigators over the next three years to build upon existing strengths in human genetics and developmental biology.

We are seeking outstanding applicants at the level of **ASSISTANT and/or ASSOCIATE PROFESSOR** in the broad fields of genetics and functional genomics, including but not limited to human genetics, genetic approaches to complex disease, population genetics, behavioral genetics, regenerative medicine, developmental genetics, and animal models of human disease and development. Our Department has a strong history in human genetics and resources, such as the Utah Population Data Base, that are unique in the world. These resources have created a highly productive and collaborative environment between researchers, clinicians, and the community.

Creative scientists with a record of achievement and commitment to excellence in both research and teaching are encouraged to apply. Successful candidates will receive a substantial startup package and enjoy a stimulating and supportive research environment.

Applicants should submit curriculum vitae, a summary of research plans, relevant reprints and/or preprints, and three letters of reference to:

**Dr. Mario R. Capecchi**
**Co-Chair, Department of Human Genetics**
**Howard Hughes Medical Institute**
**University of Utah School of Medicine**
**15 North 2030 East, Room 2130**
**Salt Lake City, UT 84112-5330**

Application materials, including letters of reference, should be submitted by November 9, 2007.

*The University of Utah is an Equal Opportunity/Affirmative Action Employer, encourages nominations and applications from women and minorities, and provides reasonable accommodation to the known disabilities of applicants and employees.*

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### DIRECTOR of BASIC SCIENCE RESEARCH
**SimmonsCooper Cancer Institute**
**Southern Illinois University**

The SimmonsCooper Cancer Institute (SCCI) is recruiting a scientific leader to provide vision and administrative oversight to its basic science research program. At present, eight faculty members comprise the SCCI Basic Science Program. A new cancer institute building with state-of-the-art facilities is currently under construction and should be completed within one year.

The successful candidate for this leadership position will possess a Ph.D. and/or M.D., significant experience in research, mentoring and administration, and external funding for basic science research relevant to oncology. Responsibilities for this position include participation in the curriculum for undergraduate medical students and in the graduate program for molecular biology, microbiology, and biochemistry. The appointment will be a tenure-track position at the level of **ASSOCIATE/FULL PROFESSOR** in an appropriate academic department, with a cross appointment to the institute. Funding for this position is provided by the Southern Illinois University School of Medicine.

Applicants should submit a letter of interest, curriculum vitae with a history of external funding, a description of research accomplishments and plans, and the names and contact information for three professional references to:

**Mr. Garrison C. Veicht**
**Administrator, SimmonsCooper Cancer Institute**
**at Southern Illinois University**
**P.O. Box 19677**
**Springfield, IL 62794-9677**

*This position has been designated security-sensitive and employment is contingent upon the results of a criminal background investigation. SIU is an Equal Opportunity Employer. Women and minorities are encouraged to apply.*

## POSITIONS OPEN

### FACULTY POSITIONS
**Human Molecular Genetics Program,**
**Children's Memorial Research Center**
**and Northwestern University**
**Chicago, Illinois**

Applications are solicited for **ASSISTANT PROFESSOR** level positions in the Human Molecular Genetics Program at Children's Memorial Resesarch Center (CMRC). We seek Ph.D. and M.D./Ph.D. candidates with outstanding graduate and postdoctoral training, a very strong publication record, the potential to attract external funding, and a commitment to develop an interactive research program. New laboratory space and state-of-the-art equipment are in place. Startup packages will be generous and successful applicants will be eligible for tenure-track faculty positions in the Department of Pediatrics, Feinberg School of Medicine, Northwestern University. Candidates with research interests in all areas of human genetics will be considered, including human genetic disease and models thereof, gene structure and function, regulation of gene expression, chromatin structure and modification, and bioinformatic approaches to human genome analysis.

Please send curriculum vitae, a statement of research interests, contact information of three references, and PDF files of most relevant publications care of: **Chris Pomeroy, Human Molecular Genetics Program, Children's Memorial Research Center, 2430 N. Halsted Street, Chicago, IL 60614 U.S.A. E-mail: c-pomeroy@northwestern.edu.**

Review of applications will continue until positions are filled.

*Northwestern University is an Affirmative Action/Equal Opportunity Employer. Hiring is contingent upon eligibility to work in the United States. Women and minority candidates are strongly encouraged to apply.*

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### FACULTY POSITIONS
**The Fred Hutchinson Cancer Research Center**

The Division of Human Biology at the Fred Hutchinson Cancer Research Center is soliciting applications to fill two **JUNIOR** faculty positions. We are especially interested in candidates using genomic, proteomic, genetic, and/or other innovative approaches to study the pathogenesis of cancer or other human diseases. Applicants with a particular interest in translational research are encouraged to apply.

The Human Biology Division fosters interdisciplinary, collaborative research at the interfaces of basic, clinical, and population sciences in order to further our understanding of human biology, cancer, and other complex human diseases.

The Division occupies state-of-the-art research laboratories on a new lakeside campus. The Center offers outstanding shared resources, including DNA array, imaging, and proteomics facilities. The Center has active training programs for graduate students and postdoctoral fellows and offers exceptional opportunities for scientific interactions with other investigators in the Seattle area.

Additional information about the Division can be found at **website: http://www.fhcrc.org/science/humanbio/.**

Candidates should send curriculum vitae, a concise statement of research plans, and three letters of reference to: **Human Biology Faculty Search Committee, Fred Hutchinson Cancer Research Center, Division of Human Biology, Mailstop: C3-168, 1100 Fairview Avenue North, P.O. Box 19024, Seattle, WA 98109-1024.** The application deadline is October 31, 2007.

*The Fred Hutchinson Cancer Research Center is an Equal Opportunity Employer committed to work force diversity. Applications from female and minority candidates are strongly encouraged.*

## HUMAN GENETICIST
### Tenure-Track/Tenure Position

The newly formed intramural Laboratory of Translational Genomics (LTG) in the Division of Cancer Epidemiology and Genetics (DCEG), National Cancer Institute (NCI), National Institutes of Health (NIH), Department of Health and Human Services (DHHS), is recruiting two tenure-track/tenured investigators. The mission of the LTG is to investigate the genetic basis of strong association signals identified by candidate gene approaches, linkage analyses in high-risk families, or genome-wide association studies (GWAS), particularly loci identified by the ongoing Cancer Genetic Markers of Susceptibility (CGEMS) program involving GWAS of several major cancers. Investigators in the LTG are expected to develop an independent research portfolio in cancer genomics focused on (1) fine mapping and re-sequencing of loci relevant to cancer susceptibility and/or outcomes, (2) investigation into the causal gene variants that provide biological plausibility for each locus, and (3) bioinformatic analyses of publicly available datasets derived from germline annotation of genetic variation and somatic alterations in cancers. Each investigator is expected to leverage the NCI resources in molecular epidemiology, high-throughput genotyping and whole genome scans, biostatistics and bioinformatics, as well as in basic and clinical sciences. The incumbent will receive research support for developing a state-of-the-art genomics laboratory, and recruiting two post-doctoral fellows/bioinformaticians and a technician.

Applicants must have an M.D. and/or Ph.D. in a relevant field, extensive post-doctoral experience, and a record of publications demonstrating potential for creative independent research in human cancer genetics. Facility with bioinformatics databases and high dimensional data are highly desirable along with strong communication skills. Interested individuals should send a cover letter, curriculum vitae and a brief summary of research accomplishments and goals, along with copies of three to five publications or preprints, and three letters of reference to:

**Ms. Judy Schwadron, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd. EPS/8073, Bethesda, MD 20892**.

Recommendations can be included with the package or sent directly by the recommender to Ms. Schwadron. Candidates should submit applications by **October 15, 2007**; at this time, the committee will begin to look at suitable candidates. However, the search will continue until qualified scientists are found. Additional information about staff and ongoing research in the NCI Division of Cancer Epidemiology and Genetics is available at **http://www.dceg.cancer.gov**. Please contact **Dr. Stephen Chanock (phone 301-435-7559 at chanocks@mail.nih.gov) or Dr. Peggy Tucker (phone 301-496-8031 at tuckerp@mail.nih.gov)** for questions about the position(s).

## Tenure-Track Investigator Position in the Laboratory of Immunology

The Laboratory of Immunology (LI), Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health invites applications for a tenure-track investigator position in immunology. Applicants should have a Ph.D., M.D., or equivalent degree; an outstanding record of postdoctoral accomplishment; and an interest in any area of biomedical research related to immunology.

Specifically, we seek a highly creative individual who will establish an independent, forward-looking, world class research program that takes full advantage of the special opportunity afforded by the stable, long-term funding of the Intramural Research Program at NIH. She/he should be interested in developing and applying novel approaches to the study of problems of major biological and /or medical importance, which could include a major clinical research effort. There are ample opportunities to participate in trans-NIH initiatives involving technology development, translational investigation, and multidisciplinary science.

Generous ongoing support for salary, technical personnel, postdoctoral fellows, equipment, and research supplies will be provided. Available cores or collaborative facilities include flow cytometry, advanced optical imaging, microarray generation and analysis, computational biology, production of transgenic and gene- manipulated mice, chemical genomics and support for projects involving RNAi screening. In addition to an outstanding international postdoctoral community, a superior pool of graduate and undergraduate students is available to the successful applicant.

NIAID's Laboratory of Immunology has a distinguished history of accomplishment in immunology. We strongly encourage outstanding early career investigators who can continue and enhance this record of achievement to apply. Current LI principal investigators are Ronald Germain, Michael Lenardo, Rose Mage, David Margulies, William Paul, Ethan Shevach and Tsan Xiao.

**Application Process:** To apply, e-mail your CV, bibliography, and an outline of a proposed research program (no more than two pages) to **Ms. Wanda Jackson at jacksonwa@niaid.nih.gov or mail to Ms. Wanda Jackson, 10 Center Drive MSC 1356, Building 10, Rm. 4A-26, Bethesda, Maryland 20892-1356. E-mail is preferred**.

**Reference Letters:** Three letters of recommendation must be sent directly from the referees to **Ms. Wanda Jackson via e-mail or U.S. mail**. Please refer to **Ad #016** on all communications. Further information about this position may be obtained by contacting **Dr. William Paul (301 496-5046; wpaul@niaid.nih.gov)**. Applications must be received by **October 19, 2007**.

A full package of benefits (including retirement, health, life and long term care insurance, 401-k plan) is available. Women and minorities are especially encouraged to apply. U.S. citizenship is not required.


**NIEHS**
National Institute of Environmental Health Sciences
National Institutes of Health

## Staff Scientist in Structural Biology
**Research Triangle Park, North Carolina**

The Laboratory of Structural Biology at the National Institute of Environmental Health Sciences is recruiting a staff scientist in support of the Macromolecular Structure Group headed by Dr. Traci Hall. The recruit will be responsible for assisting with oversight of structural and biochemical efforts by the group. In particular, the incumbent will focus efforts on long-term projects aiming to determine structures of large macromolecular complexes involved in post-transcriptional gene regulation and to create and use designed RNA-binding proteins. The successful candidate is expected to work with minimal guidance, personally execute experiments, carry the research to publishable stages, and work on these and other projects as defined by the group leader, Dr. Hall.

Minimum qualifications include a doctoral degree, successful completion of postdoctoral training, strong publication record and experience in X-ray crystallography, biochemistry and molecular biology, emphasizing experience with protein expression and purification, macromolecular crystal structure determination, and quantitative biochemical analyses of macromolecular complexes. Familiarity with mechanisms of post-transcriptional gene regulation and background in structural and functional studies of RNA-binding proteins is desirable.

For additional information on the position or research emphasis, contact Dr. Traci Hall at 919-541-1017 or hall4@niehs.nih.gov. For details regarding on-going projects in the laboratory, please visit website http://www.niehs.nih.gov/research/atniehs/labs/lsb/ms/index.cfm. Applications from women and minorities are particularly encouraged. Salary will be commensurate with experience. To apply, submit a curriculum vitae, bibliography, brief statement of research experience and interests and arrange for three letters of recommendation to be sent by **October 5, 2007** to the following address. Applications received after that date will be considered as needed:

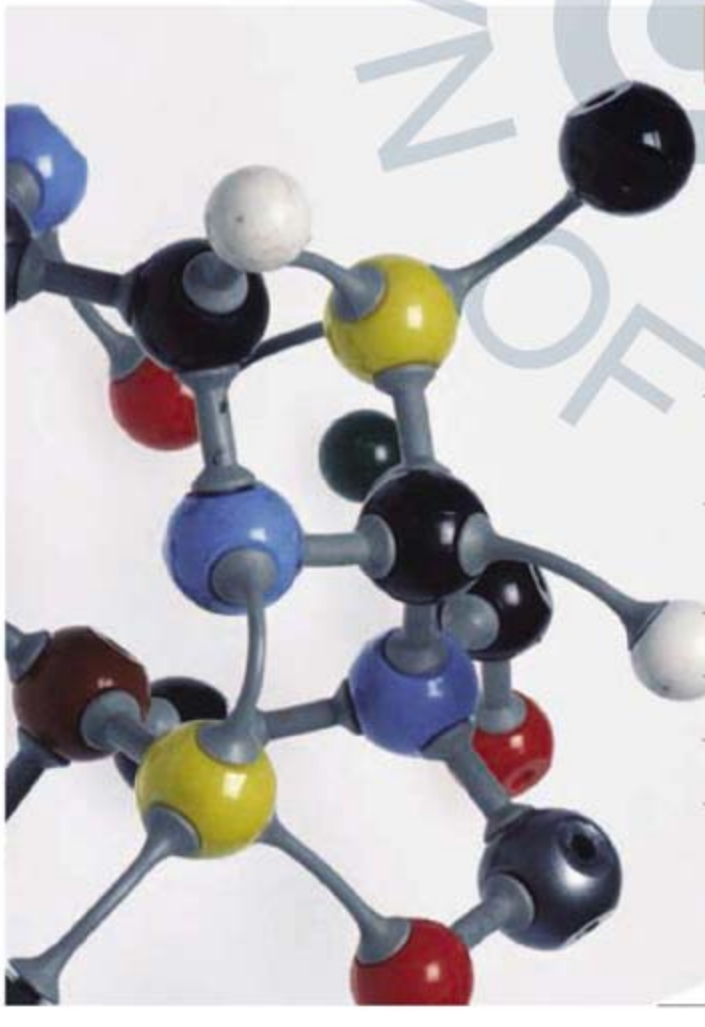
Ms. Cindy Garrard (DIR07-04)
NIEHS Division of Intramural Research
P.O. Box 12233, Maildrop A2-06,
111 Alexander Drive, Room A204
Research Triangle Park, NC 27709
e-mail: **dir-appls@niehs.nih.gov**

*DHHS and NIH are Equal Opportunity Employers*

## Post Doctoral Fellowship
## Development of Novel Gene Regulatory Mechanisms for AAV Gene Therapeutics

Our laboratory is focused on the development of adeno-associated virus-based gene therapeutics for the treatment of ocular diseases such as retinitis pigmentosa and macular degeneration. The clinical development of promising drugs of this type is severely hampered by the lack of switch technology that could be used to modulate gene expression or to shut it off in the case of an adverse event. We are looking for a creative and energetic Post Doctoral Fellow to work with an interdisciplinary team focused on the development and refinement of novel switch technologies for clinical use. We are currently interested in small molecule regulation of protein expression at all levels (transcriptional, post-transcriptional, translational) and post-translational regulation of protein activity. The successful candidate will have an appropriate background in regulation of gene/protein expression or in protein engineering and design. Experience with RNA-based switch mechanisms is particularly desirable. Most importantly, the candidate must demonstrate the ability to integrate ideas and to innovate successfully.

Benefits include health insurance for the trainee and his/her family and travel to one meeting each year. In addition, the NIH Fellows Committee and the Office of Intramural Training and Education sponsor a wide range of career development and social activities. Applications should be sent to: **Dr. Peter Colosi, National Eye Institute, 5625 Fishers Lane, Room 1S-16, Rockville, MD 20852 or Email: colosip@nei.nih.gov.**



# Postdoctoral Research Training at NIH

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Office of Intramural Training and Education

FAS Center for Systems Biology

## Harvard University
## FAS Center for Systems Biology
## Faculty Positions

The Faculty of Arts and Sciences (FAS) at Harvard University is creating a Center to bring together scientists involved in research on systems biology, broadly defined as the study of how complex properties arise in biological systems from the interactions of component parts. We are particularly interested in candidates from the field of computational biology and theory but will also consider applications in the fields of the emergent properties of biological systems, bioengineering and technology development for biology. The FAS Center for Systems Biology (**http://sysbio.harvard.edu/csb**) will foster interactions across disciplinary boundaries, with faculty from a spectrum of academic departments and the Bauer Fellows housed in common research space. This effort will work in close collaboration with the Department of Systems Biology at Harvard Medical School to build a campus-wide community of faculty, postdoctoral fellows, and students working on systems biology.

We expect to make as many as ten new appointments over the next few years. Each new faculty member will hold an academic appointment in a participating department, such as Molecular and Cellular Biology, Organismic and Evolutionary Biology, Physics, Chemistry and Chemical Biology, or the Division of Engineering and Applied Sciences (which includes Applied Mathematics and Computer Science). Appointments in relevant Medical School Departments such as the Department of Systems Biology are also possible. Links to other resources at Harvard including the Bauer Core Resource, the Center for Nanoscale Systems, the Broad Institute, and the Center for Brain Science will provide facilities and opportunities for collaborative research and technology development. We are particularly interested in applications for faculty positions at the rank of assistant professor (tenure track), but will consider exceptional candidates at other ranks.

Applications are due by **December 16, 2007**. Please submit a curriculum vitae, research proposal (<5 pages), summary of previous research accomplishments (<2 pages), copies of 1-3 publications, and 3 letters of recommendation by email to **sysbio_search@lsdiv.harvard.edu**. All files must be submitted electronically in pdf or Word format.

*Applications from, or nominations of, women and minority candidates are encouraged. Harvard is an Affirmative Action/Equal Opportunity Employer.*

## Faculty Position in Cell Biology
## University of Texas Southwestern Medical Center at Dallas

The Department of Cell Biology at The University of Texas Southwestern Medical Center at Dallas seeks to appoint exceptional scientists who are experts in the fields of general cell biology, live cell imaging, cryoEM, or electron tomography to the position of Assistant Professor (tenure track). Candidates must have a Ph.D. or M.D. and be doing cutting edge research at the interface between cell and molecular biology in such areas as: organization of macromolecular complexes, molecular interactions in living cells, spatial organization of signal transduction and cellular basis of tissue organization. The excellence of the individual candidate will take precedence over the area of special interest. The successful candidate will join an internationally recognized Cell Biology faculty at a top rated medical institution and receive both a competitive salary and an exceptional start-up package.

For more information, visit the Cell Biology web site at: **http://www8.utsouthwestern.edu/utsw/cda/dept25128/files/34664.html**

Applicants should email their curriculum vitae, the names of three references, and a brief description of their research goals to the attention of **Dr. Richard G. W. Anderson** at **cb.recruitment@utsouthwestern.edu**.

*The University of Texas Southwestern Medical Center is an Affirmative Action/Equal Opportunity Employer. Women and minority candidates are encouraged to apply.*

## Massachusetts Institute of Technology

## The Clare Boothe Luce Postdoctoral Fellowships for Women in Energy at MIT

The Massachusetts Institute of Technology (MIT) Energy Initiative invites applications for The Clare Boothe Luce (CBL) Postdoctoral Fellowships for Women in Energy at MIT. Support from the Henry Luce Foundation will provide two exceptional women with two-year postdoctoral fellowships for interdisciplinary study focused on energy topics beginning in the fall of 2008. The selected Fellows will be top scholars from disciplines in which women are particularly underrepresented, and which are encompassed by the MIT Energy Initiative (MITEI). This is an opportunity for CBL Fellows to be part of a flagship initiative launched by MIT's President Susan Hockfield to address the science, technology, policy, and systems design issues required to meet the global energy challenge. CBL Fellowships will provide the scholars with stipends at the highest level of MIT's most prestigious postdoctoral fellowships, and allowances for childcare where appropriate, moving expenses and travel to conferences. CBL Fellows will have the option to teach or serve as teaching assistants for a semester, and to mentor graduate students and undergraduate students who participate in faculty research programs. This optional component of the fellowship program will provide CBL Fellows with valuable experience that will aid them in future faculty positions.

To be eligible for the CBL Fellowships in Energy at MIT, candidates must complete their PhD no earlier than June 2006 and no later than August 31, 2008. Candidates must have their PhD and be working in a field where women are particularly underrepresented. Some specific areas of interest include but are not limited to electrical engineering and computer science, mechanical engineering, nuclear engineering and physics.

Candidates must identify an MIT advisor who will support their application. Interested individuals are invited to submit a short proposal (3-5 pages) along with a curriculum vitae, letter of recommendation from the prospective MIT faculty advisor, and two additional letters of support from faculty members of the applicant's choice. The proposal should briefly outline the candidate's interdisciplinary research interests and career goals in the energy field, and indicate the applicant's experience and interest in teaching. Please include the emails, street addresses, and telephone numbers of the applicant, MIT advisor and two references. Submit application materials in writing to the attention of Robin Elices, MIT Energy Initiative, 77 Massachusetts Avenue, Building E40 Room 465, Cambridge, MA 02139. The complete application, including reference letters, must be received by November 9, 2007 to receive full consideration. Announcement of the selected Fellows is planned for December, 2007. Additional information is available at web.mit.edu/mitei.

**http://web.mit.edu**

## ASSISTANT PROFESSOR
### DEPARTMENT OF NEUROBIOLOGY AND BEHAVIOR UNIVERSITY OF CALIFORNIA, IRVINE

Applications are invited for a tenure-track position at the level of ASSISTANT PROFESSOR. The Department of Neurobiology and Behavior engages in interdisciplinary approaches to the study of neurobiology, with an emphasis on neural plasticity and behavior. Current Departmental research themes include: (i) mechanisms underlying age-related neuro degenerative disorders, (ii) learning and memory, (iii) sensory and integrative neuroscience (including molecular/genetic, synaptic and systems levels), (iv) development, (v) neurocomputation, and (vi) the neurobiology of substance abuse. Preference will be given to applicants whose research integrates with one or more of those themes and whose approach is at the systems level, preferably in behaving animals.

Please submit by **November 1, 2007**, curriculum vitae, description of research interests, and the names and addresses of three potential referees. Please see the URL: **http://jobs.bio.uci.edu/showopenjobs_tenure.cfm** for application instructions under "Department of Neurobiology and Behavior."

*The University of California, Irvine is an Equal Opportunity Employer committed to excellence through diversity and strongly encourages applications from all qualified applicants, including women and minorities.*

EMBL

*The European Molecular Biology Laboratory is searching for Group Leaders. EMBL offers a highly collaborative, uniquely international culture. It fosters top quality, interdisciplinary research by promoting a vibrant environment consisting of young, independent researchers with access to outstanding graduate students and postdoctoral fellows. EMBL is an inclusive organisation and provides excellent social benefits and child care facilities.*

# Research Group Leader Opportunities

## EMBL – EUROPEAN BIOINFORMATICS INSTITUTE (EBI), HINXTON, UK

Ref. no. 07/121/EBI

The EMBL-EBI, located near Cambridge, UK on the Welcome Trust Genome Campus, is a global centre for molecular biology data, hosting the very large sequence, structure and expression data resources in Europe as well as seven research groups. We are seeking a dynamic computational biologist, with a proven track record, to establish a new research group to complement our current programme. At the EBI, research is pursued in many different aspects of biology, exploiting and helping to interpret the biological data held in the databases. Currently research topics include sequence analysis, computational genomics, phylogeny, structural biology, regulatory control networks, functional genomics, neurobiology and literature/text mining. In addition, research activities are an important part of several of the large data resource teams, which also provide services. We are keen to expand our research into the areas of comparative genomics and large scale sequence analysis, chemo-informatics and population genetics, but will favour outstanding candidates from any area of computational biology. The candidate will join a strong and supportive group of young research group leaders and will interact closely with the large database teams, benefiting from their technical expertise and scientific knowledge. EMBL-EBI provides an excellent research environment including computational facilities and support.

## EMBL HEIDELBERG, GERMANY

### STRUCTURAL AND COMPUTATIONAL BIOLOGY

Ref. no. 07/122/SCB

The unit combines the use of different structure determination techniques (X-ray, NMR, cryo-EM, EM tomography) with concepts from computational and chemical biology to provide detailed spatial and temporal descriptions of various biological systems across different scales of resolution (from molecules to cells). The unit seeks to recruit a candidate in the area of biochemistry, systems biology or chemical biology. The successful candidate will be integrated into the collaborative network of EMBL groups and should pursue experimental approaches complementary to those existing in the SCB unit. Example research areas include light microscopy and fluorescence techniques for in vitro and in vivo characterisation of macromolecular assemblies, protein or small molecule interaction mapping, labelling technologies, dynamics of molecular machines or metabolome research.

### DEVELOPMENTAL BIOLOGY

Ref. no. 07/123/DB

The unit studies the development of multicellular organisms, from the cellular to the whole organism level, combining genetic, cell-biological, biochemical, genomic/proteomic, computational and live-imaging approaches. Current research topics include cell fate specification and polarity, morphogenesis and organogenesis, neurodevelopment, evolution, gene regulatory networks and comparative and functional genomics. We are seeking outstanding candidates addressing fundamental questions in developmental biology that complement our existing strengths.

### GENE EXPRESSION – PROTEOMICS

Ref. no. 07/124/GE

EMBL plans to expand its activities in proteomics and biological mass spectrometry by recruiting an outstanding candidate in this area. EMBL has a strong tradition in proteomics and many research groups that apply mass spectrometry to cutting edge biological questions, including metabolite-protein interactions across the proteome (Anne-Claude Gavin), bacterial proteomics (EMBL Hamburg and Structural and Computational Biology Units) and eukaryotic organelle proteomics (Lars Steinmetz). EMBL also has an excellent proteomic core facility that provides routine mass spectrometry service to biological research groups. We therefore particularly encourage candidates that develop new technologies in mass spectrometry with applications in biology, for example posttranslational protein modifications, quantitative analysis of macromolecular complexes, quantitative or dynamic proteomics. We also welcome candidates with demonstrated excellence in other areas of biological proteomics.

To apply, please email a CV, three references and a concise description of research interests and future plans, quoting the corresponding ref. no. in the subject line, to: application@embl.de by October 28th, 2007.

For further details please visit **www.embl.org**

# The School of Biology

Georgia Tech College of Sciences

seeks truly outstanding junior and senior level faculty to complement growing strengths in systems and integrative biology (http://www.biology.gatech.edu/). The Georgia Institute of Technology is consistently ranked as one of the top educational/research institutions in the nation. The School of Biology has experienced dramatic expansion in recent years and Georgia Tech is committed to the continued growth and integration of the biological sciences with existing and emerging strengths in quantitative/computational sciences, nanotechnology, nanobiology and engineering.

**Experimental Systems Biology:** We are searching for individuals at all ranks with outstanding records of research accomplishments. We are particularly interested in identifying individuals taking a systems approach to the analysis of development who can leverage existing/emerging strengths in the areas of computational/quantitative biology, structural biology, genomics, transcriptomics, proteomics and metabolomics. **Contact: Professor and Chair John McDonald.**

**Computational Biology:** We are interested in both senior and junior level investigators who employ computational and quantitative approaches to the analysis of integrated biological systems across multiple levels of scale. Specific research areas include the analysis of cellular networks, such as gene regulatory networks and biochemical pathways, the integration of heterogeneous sources of biological data, the study of genome variation within and between species, evolutionary dynamics and the many scale computational modeling of biological systems. **Contact: Associate Professor I. King Jordan.**

**Environmental Microbiology:** We are searching for an environmental microbiologist as part of the expansion in microbial systems biology. While it is anticipated that the position will be filled at the junior level, exceptionally qualified individuals at any rank are invited to apply. Areas of research focus may include metabolomics, proteomics metagenomics and synthetic biology. **Contact: Associate Professor Patricia Sobecky.**

Candidates should forward a letter of application, a full curriculum vitae and the contact information for four references to the indicated contact individuals.

School of Biology
Georgia Institute of Technology
310 Ferst Drive
Atlanta, GA 30332

Review of Applications will begin
October 1, 2007

*Georgia Tech is a unit of the University System of Georgia and an Affirmative Action/Equal Opportunity Employer and requires compliance with Immigration Control Reform Act of 1986.*

## ORGANIC CHEMISTRY
## UNIVERSITY OF CALIFORNIA AT SANTA BARBARA

The Department of Chemistry and Biochemistry at UC Santa Barbara invites applications for faculty positions in organic chemistry. Applicants at the Assistant Professor level are especially encouraged to apply within all areas of organic chemistry, including but not limited to bioorganic chemistry, organic materials, organic methods, organic synthesis, physical organic chemistry and chemical biology. A Ph.D. is required at the time of appointment. The selected candidates are expected to establish a vigorous well-funded research program and to teach in the graduate and undergraduate levels.

Applicants should ensure that a curriculum vitae, a summary of research plans, a statement of teaching philosophy, and three letters of recommendation are sent to the *Organic Professor Search Committee* as PDF attachments to **tops@chem.ucsb.edu**. Only applications submitted via email by **November 1, 2007** will be reviewed. However, the search will continue until at least two positions are filled. Appointments can become effective as early as July 1, 2008.

*UCSB is an Equal Opportunity/Affirmative Action Employer and the Department is especially interested in candidates who can contribute to the diversity and excellence of the academic community through research, teaching and service.*

## Tenure-track Faculty Position in Biogeoscience
## University of Minnesota
## Department of Geology and Geophysics

The Department of Geology and Geophysics at the University of Minnesota-Twin Cities invites applications for a tenure-track faculty position in biogeoscience. Potential research areas include: microbe/mineral interactions; microbe/groundwater interactions; microbial evolution and biochemistry; the role of organisms in geological processes; organic geochemistry and paleoenvironments; biogeochemical cycling; origin and early evolution of life on Earth; analytical paleobiology; and astrobiology. We would be especially interested in candidates whose work would complement and extend our current strengths in stable-isotope paleoecology, paleoclimatology, limnogeology, environmental magnetism, low-temperature geochemistry, geofluids and environmental geology, marine geochemical modeling and hydrothermal vents, surface-lithosphere interactions, and Earth-surface dynamics. We are open to applicants whose training is outside the Earth sciences, but the candidate would be expected to concentrate on Earth sciences problems if hired. The successful candidate is expected to initiate and maintain a strong externally funded research program.

The N.H. Winchell School of Earth Sciences includes the Limnological Research Center; three NSF-funded research centers: the National Lacustrine Core Repository, the National Center for Earth-surface Dynamics, and the Institute for Rock Magnetism; the Minnesota Geological Survey; and excellent laboratories in geochemistry and experimental mineral physics and petrology. Other resources include the St Anthony Falls Laboratory (**www.safl.umn.edu**), Materials Characterization Facility (**www.charfac.umn.edu**), Supercomputer Institute (**www.msi.umn.edu**), Digital Technology Center (**www.dtc.umn.edu**), BioTechnology Institute (**www.bti.umn.edu**), OMNI, a multi-disciplinary organization for Minnesota Nanotechnology Initiatives (**www.nano.umn.edu**), and the Initiative for Renewable Energy and the Environment (**www.umn.edu/iree/**). Further information concerning the Department, its faculty and their research programs can be obtained at www.geo.umn.edu.

The department encourages and rewards innovative research and excellence in teaching. Teaching duties reflect the expertise of the candidate and include both undergraduate and graduate levels. Appointment will most likely be at the rank of assistant professor and could begin as early as August 2008. A Ph.D. degree must be earned by the time of the appointment. The review of completed applications will begin **October 15, 2007** and continue until an appointment is made. Complete applications, which may be on paper or electronic, must include (1) curriculum vitae, (2) complete list of publications, (3) statement of research interest, (4) statement of teaching interests, and (5) names, addresses and e-mail addresses of at least four references. All candidates must complete an online application via the University of Minnesota employment system at: **https://employment.umn.edu** (requisition number **150214**). Application materials may be sent to: **Chris Paola, Biogeoscience Search Committee Chair, Department of Geology and Geophysics, University of Minnesota, 310 Pillsbury Dr. S.E., Minneapolis, MN 55455 USA; cpaola@umn.edu.**

*The University of Minnesota is an Equal Opportunity Educator and Employer.*

# VCU

**Virginia Commonwealth University**

## Faculty Position in Medicinal Chemistry

The Department of Medicinal Chemistry, School of Pharmacy, VCU, invites qualified candidates to apply for a tenure-track position at the Assistant or Associate Professor level available immediately. Preference will be given to those with research programs in any area of medicinal chemistry. The most successful candidate will have a funded program and publications in an area complementary to departmental interests. Also preferred is experience in classroom teaching of medicinal chemistry at the professional and graduate levels.

The position will remain open until filled, and applications must include a detailed curriculum vitae, a description of research achievements, a statement of future research objectives, funding history, and the names (and contact information) of four references.

Applications should be submitted to **Dr. Glen E. Kellogg, Search Committee Chair, Department of Medicinal Chemistry, School of Pharmacy, Box 980540, VCU, Richmond, VA 23298**. Email: **glen.kellogg@vcu.edu**.

*Virginia Commonwealth University is an Equal Opportunity, Affirmative Action Employer. Women, minorities and persons with disabilities are encouraged to apply.*

GKSS
FORSCHUNGSZENTRUM
IN DER HELMHOLTZ-GEMEINSCHAFT

C A U
Christian-Albrechts-Universität zu Kiel

Unternehmen Großforschung

Grundlagen für morgen

By means of a joint appointment process with the Christian Albrechts University of Kiel (Faculty of Mathematics and Natural Sciences), GKSS-Forschungszentrum Geesthacht GmbH is seeking to fill the position of

# Head

of the department of

## Structural Research of New Materials at the Institute of Materials Research

The place of work is in Geesthacht.

Associated with the position is a

## Professorship (on the basis of grade W2) for Structural Research of Materials at the Christian Albrechts University of Kiel.

The Institute of Materials Research develops lightweight materials on the basis of titanium aluminides and magnesium and creates evaluation methods for fracture and damage mechanics as well as joining technologies for materials and components. The individual appointed to the position should intensify the activities in the area of materials characterisation with neutrons and synchrotron radiation. Applicants should show strong commitment to research and teaching and be internationally recognised experts in the field of materials research with neutrons and/or synchrotron radiation at large-scale facilities. Prospective jobholders are expected to take on a leading role in the innovative enhancement of instruments and methods for conducting scattering experiments in materials research. The applicant is also required to have leadership skills and be willing to seek external funding. In addition, he or she will have to teach courses in physics. It is also expected that the future jobholder will actively participate in the collaboration with DESY in Hamburg regarding the use of the synchrotron radiation sources (DORIS III, PETRA III and XFEL) as well as with FRM-II in Munich concerning the use of neutrons for materials research.

Applicants should have a habilitation degree or comparable scientific qualifications as well as sufficient teaching experience. Please refer to Art. 63 Section 1 of the Higher Education Act of the State of Schleswig-Holstein. Other preconditions include excellent skills in performing scientific work and the willingness to cooperate closely with other departments at the Institute of Materials Research at GKSS and with the Christian Albrechts University of Kiel. It would moreover be advantageous if the applicant is willing to work together with GKSS's Institute of Polymer Research in the area of structural materials and biomaterials research, and if he or she has worked for several years in an industry-related research environment.

The Christian Albrechts University of Kiel and GKSS-Forschungszentrum Geesthacht GmbH wish to increase the proportion of women professors in research and teaching positions, which is why adequately qualified female scientists are particularly encouraged to apply.

The University and GKSS-Forschungszentrum Geesthacht strive to increase the employment of handicapped people. Preference will therefore be given to severely disabled persons with the proper qualifications.

For additional information, please contact Prof. Andreas Schreyer (andreas.schreyer@gkss.de).

The deadline for applications is **October, 30th, 2007**. Please submit your applications along with the usual documents (C.V., description of your scientific career, copies of your certificates/degrees, list of publications, copies of three of your publications, description of your teaching experience, and a brief overview of your research objectives) in English to: **Dekan der Mathematisch-Naturwissenschaftlichen Fakultät, Christian-Albrechts-Universität, 24098 Kiel, Germany**.

University of California
LAWRENCE LIVERMORE NATIONAL LABORATORY
*Science in the National Interest*

## LAWRENCE POSTDOCTORAL FELLOWSHIP

The Lawrence Livermore National Laboratory (LLNL) has openings available under its Lawrence Fellowship Program. This is a highly desirable, prestigious postdoctoral position with ample resources and freedom to conduct cutting-edge research in a field of the candidate's choice. The duration of the Fellowship is up to three years. Typically two to four openings are available each year. Fellowships are awarded only to candidates with exceptional talent, credentials and a track record of research accomplishments.

Candidates will do original research in one or more aspects of science relevant to the mission and goals of LLNL which include: Physics, Applied Mathematics, Computer Science, Chemistry, Material Science, Engineering, Environmental Science, Atmospheric Science, Geology, Energy, Lasers and Biology. Successful candidates may participate in experimental or theoretical work at LLNL, and will have access to LLNL's extensive computing facilities, specialized laboratory facilities and field equipment. A senior scientist will serve as a mentor to each of the Fellows. The candidates will receive full management and administrative support. The salary is $8,092/mo.

Please refer to our web page **http://fellowship.llnl.gov** for eligibility requirements and instructions on how to apply. When applying and prompted, please mention where you saw this ad. The deadline for application is November 2, 2007. LLNL is operated by the University of California for the National Nuclear Security Administration/Department of Energy. We are an Equal Opportunity Employer with a commitment to workforce diversity.

**Lawrence Livermore National Laboratory**

**http://fellowship.llnl.gov**

## Stanford University Molecular/Cell Biologist Faculty Position

The Department of Biological Sciences at Stanford University welcomes applicants for a tenure track faculty position at the Assistant Professor rank. We seek individuals studying basic problems in molecular biology and cell biology, at any level from molecules to tissue organization, with the goal of providing new mechanistic insights. We are particularly interested in applicants who address these problems with innovative approaches such as biological imaging, proteomics and metabolomics, and/or systems biology. Applicants are expected to develop a vigorous research program and to participate in both undergraduate, graduate, and postdoctoral education and training. For information about the Department consult our web page: **http://biology.stanford.edu/**.

Applicants are requested to provide a cover letter, a curriculum vitae including list of publications, a statement of research accomplishments and future research plans, a description of teaching experience, and three letters of recommendation. Applicant materials must be received by **November 1, 2007**. The appointment would begin September 1, 2008. Interested candidates should apply online at **AcademicJobsOnline.Org**.

*Stanford University is an Equal Opportunity Employer and is committed to increasing the diversity of its faculty. It welcomes nominations of and applications from women and minority groups, as well as others who would bring additional dimensions to the university's research, teaching and clinical mission.*

# INSTITUTE DIRECTOR

## THE INSTITUTE ON THE ENVIRONMENT

The University of Minnesota invites applications and nominations for the position of founding Director of the University's new Institute on the Environment. This competitive center of excellence will bring together multidisciplinary research teams to work on global environmental issues that have regional significance. The Director will exercise University-wide leadership in formulating policies and providing educational programs that engage the University in responding to statewide, national and international environmental issues. Candidates must have an advanced degree in a relevant field, a significant record that combines interdisciplinary research and scholarship activity with administrative or managerial experiences, credentials that warrant a tenured full professorship, and evidence of professional distinction and international recognition in their field(s). Salary, faculty rank and tenure are negotiable based upon qualifications and experience.

For a complete description and application information, please visit:
http://academic.umn.edu/provost/interdisc/environment/index.html

## UNIVERSITY OF MINNESOTA

The University of Minnesota is an Equal Opportunity Educator and Employer.

MRC Laboratory of
Molecular Biology, Cambridge

MRC Medical Research Council

## Postdoctoral Fellow

### Starting salary in the region of £24,993 per annum

The MRC Laboratory of Molecular Biology is a world-famous institution with excellent infrastructure, a collegial environment and a strong track-record in training postdoctoral fellows who have gone on to become leading scientists.

A postdoctoral fellowship (MRC Career Development Fellowship) is open for work on the structure and function of ribosomes using a combination of crystallography, electron microscopy and biochemistry.

You should have a PhD or equivalent with prior experience in at least one of the following areas: structure determination of large complexes, crystallography of RNA or biochemistry of ribosomes and translation.

This is a three year training and development position for a postdoctoral scientist who has recently completed their doctoral studies, is moving into a new research discipline or has limited experience of key transferable skills.

This is a full time post for three years with flexible working hours.
This is supported by flexible pay and a reward policy, 30 days' annual leave entitlement, an optional MRC final salary pension scheme and excellent on-site sports and social facilities.

For informal enquiries, please contact Venki Ramakrishnan (ramak@mrc-lmb.cam.ac.uk).

**For further information and to apply, please visit our website: http://jobs.mrc.ac.uk or telephone 01793 301154 quoting reference LMB07/515.**

**For on-line applications, please attach a CV and covering letter.**

**Closing date for applications is: 7 October 2007.**

**For further information about the MRC visit www.mrc.ac.uk**

The MRC is an Equal Opportunities Employer

'Leading science for better health'

## Tenure Track Positions
## Division of Nutritional Sciences

*Located in Ithaca, N.Y., Cornell University is a bold, innovative, inclusive and dynamic teaching and research university where staff, faculty, and students alike are challenged to make an enduring contribution to the betterment of humanity.*

The Division of Nutritional Sciences at Cornell University is recruiting outstanding scientists for 3 tenure-track faculty positions. The successful candidates are expected to develop extramurally funded research programs and contribute to the division's teaching mission. An advanced degree (MD, Ph.D., DVM, and/or equivalent) is required and postgraduate training highly desirable.

**ASSISTANT PROFESSOR - FUNCTIONAL MOUSE GENOMICS.** The successful candidate is expected to have expertise in genetics, biochemistry, developmental biology and/or experimental genomics and interest in exploring the interactions among nutrients, metabolism and the genome in health and disease. Areas of interest include mammalian developmental & metabolic programming, energy metabolism, epigenetics and/or complex metabolic diseases.

**ASSISTANT PROFESSOR - HUMAN METABOLISM.** The successful candidate is expected to have expertise in human nutrition and an interest in studying the interactions among nutrients, metabolism and/or genetic variation in human health and disease. Areas of interest include energy and/or lipid metabolism, maternal & child nutrition, chronic diseases, and genomics/ metabolomics/lipidomics incorporating state-of-the-art approaches.

**ASSISTANT PROFESSOR - GLOBAL HEALTH & NUTRITION.** The successful candidate is expected to have experience in global public health research and an interest in studying the biological and/or social dimensions of nutrition. Areas of expertise include but are not limited to Social Sciences, Epidemiology, Intervention Development & Evaluation and/or Infectious Disease.

These faculty searches will be conducted in concert with Cornell University's interdisciplinary initiatives in Global Health, Social Sciences and/or Life Sciences.

**To apply, please visit: http://nutrition.cornell.edu/dns7_facultyemployment.html**

The screening of candidates will begin October 5, 2007 and will continue until the positions are filled. Salary will be commensurate with the successful candidates' credentials and experience. Women and minorities are encouraged to apply.

Cornell University

*Cornell University is an Affirmative Action/ Equal Opportunity Employer and Educator.*

**http://chronicle.com/jobs/profiles/2377.htm**

## Chairperson
## School of Arts & Sciences
## Academic Year 2008-09

### Department of Biological and Environmental Sciences

New academic programs, new construction projects, including a new "state of the art" student center, and increasing student enrollment all serve to make Western Connecticut State University a vibrant, active campus serving 6,000 undergraduate and graduate students. WestConn is one of the four comprehensive universities that comprise the Connecticut State University System. The main campus is located in Danbury, 50 miles north of New York City. The University is divided into the School of Arts & Sciences, the School of Professional Studies, the Ancell School of Business and the newly created, School of Visual and Performing Arts. Additional information about WestConn is available at **www.wcsu.edu**

The Department of Biological and Environmental Sciences seeks candidates for a tenure track department chairperson at the level of Full or Associate Professor. The Department is housed in a new Science building with extensive modern facilities and equipment. There are 10 tenure-track faculty members serving 160 undergraduate biology majors, 30 M.A. students in a part-time graduate program, and a large number of nursing students in several of their required courses. We are seeking a chairperson to provide dynamic leadership and program development in biotechnology and related areas. The successful candidate will foster faculty development and scholarship, recruitment of students, and interaction with the local community, as well as manage routine administrative duties and effectively represent the department to the university administration. Some of the candidate's time will be devoted to teaching and research involving undergraduate or M.A. students.

**Qualifications:** Candidates must have a Ph.D. or equivalent terminal degree; administrative experience at the level of assistant chairperson, program director or above; six or more years full-time teaching experience in a tenure-track position; and a specialization related to biotechnology.

**Salary and Benefits:** WestConn offers competitive salaries commensurate with candidates' experience and a comprehensive benefit package. Additional information can be found on our website at:

**http://www.wcsu.edu/working**

**Application Process:** Interested candidates should submit a cover letter, a current vitae, 3 letters of recommendation, and statements of administrative philosophy, teaching philosophy, and research interests. Applications should be sent electronically to **www.facultyvitae@wcsu.edu** Please refer to search #146 in your e-mail. Review of applications begins **October 15, 2007** and continues until the position is filled.

*Western is an AA/EEO Educator/Employer.*

RUTGERS

## Assistant Professor of Cell Biology and Neuroscience

The Department of Cell Biology and Neuroscience at Rutgers, The State University of New Jersey, Piscataway, seeks to fill five tenure-track positions at the Assistant Professor level over the next five years. Applicants should have a Ph.D. and/or M.D. with a minimum of two years postdoctoral experience and evidence of continued growth as a productive researcher. Candidates in fields such as neuroscience, developmental biology, immunology, and signal transduction, from the molecular through the systems level, are strongly encouraged to apply.

The Department is located on the Rutgers Busch Campus, which is home to the majority of the University science departments, and the UMDNJ-Robert Wood Johnson Medical School. The campus is 30 minutes by car from Princeton, and one hour by train from both New York City and Philadelphia, allowing easy collaboration with other major universities in the area. Rutgers was named the top place to work for postdocs by *The Scientist* in 2003, and New Jersey is home to eight of *Money* magazine's top 100 places to live.

The successful candidate will be expected to establish an independent research program supported by external funding and to contribute to graduate and undergraduate education. The Department offers excellent facilities and a competitive start-up package. Interested individuals are encouraged to apply online through the CBN website (**http://cbn.rutgers.edu**) or send a curriculum vitae, a brief statement of research plans, and the names and addresses of three references to:

**CBN Search Committee**
**c/o Virginia Marano**
**(marano@biology.rutgers.edu)**
**Nelson Laboratories**
**604 Allison Road**
**Piscataway, NJ 08854**

*Review of applications will begin immediately on a rolling basis. Rutgers University is an Equal Opportunity/Affirmative Action Employer.*

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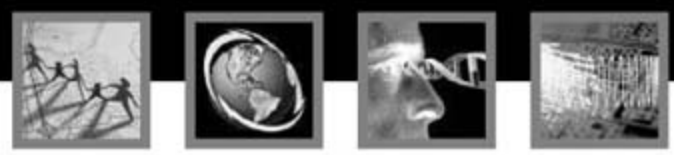
*La science en* ACTION *pour un monde en* ÉVOLUTION

INRS



## CANADA RESEARCH CHAIR — NANO-BIO-TECHNOLOGY

Competition: DS 07-02

The Center INRS Énergie, Matériaux et Télécommunications is inviting applications for a tenure-track faculty position in nano-bio-technology, associated with a senior Tier I Canada Research Chair. For information on the Canada Research Chairs program, visit **www.chairs.gc.ca**. A Tier I Chair is considered an international leader in his/her field of research. The Institut national de la recherche scientifique (INRS) is a University providing training at the graduate level (M. Sc. and Ph. D.) and is a constituent of the University of Quebec Network.

One of our main axes of strategic development is in the field of nano-bio-photonics, broadly defined as the synthesis, processing and imaging/characterization of nanosystems relevant to biology, including, but not limited to applications in health and the environment. Research topics of interest for this position may include the use of nanomaterials and processes in the broad areas of infections and cancer, both diagnosis and therapy, gene therapy, tissue repair/regeneration/engineering, the modification and characterization of biocompatible materials, advanced imaging of molecular systems from simple biomolecules to viruses to living cells (including animal studies in vivo).

The Institute is located in Varennes, on the South Shore of Montreal. More information is available on the INRS web site: **www.emt.inrs.ca**

- The successful candidate should have an outstanding record of research accomplishments and is expected to develop a strong independent research program, capitalizing on his/her international leadership in the field.
- A demonstrated track record in teaching and supervision of graduate students.
- Ability to work in a multidisciplinary team and within research networks.
- Entrepreneurial skills and proven ability to attract significant external funding.

The language of our work environment is French. Candidates whose native language is not French are encouraged to apply. The Center will provide them with all the resources necessary to facilitate their learning of the French language.

Salary and benefits are in accordance with the current collective agreement at INRS.

Interested candidates should submit a full curriculum vitæ by e-mail and registered mail, a statement of research interests (max. 3 pages), a statement of teaching philosophy, 3 representative publications, and the names and contact addresses of at least three referees **before December 14th 2007**, indicating competition **DS 07-02** to:

**Director**
**INRS-Énergie, Matériaux et Télécommunications**
**800, de la Gauchetière Ouest, suite 6900**
**Montréal (Québec) H5A 1K6**

Or to:

**concours@emt.inrs.ca**

INRS subscribes to the principle of work equality.
In accordance with Canadian immigration laws, Canadian citizens and Permanent Residents will be given priority for this position.

Université du Québec
**Institut national de la recherche scientifique**

**www.emt.inrs.ca**

ICSU
International Council for Science

**Vacancy Announcement**
**EXECUTIVE DIRECTOR**

The International Council for Science (ICSU, **www.icsu.org**), founded in 1931, is a non-governmental organization dedicated to the promotion of international science for the benefit of society. To accomplish its mission, ICSU effectively mobilizes the knowledge and resources of the international science community represented by 29 Scientific Unions and 112 National Scientific Members. ICSU also has several Interdisciplinary Bodies, which carry out global scientific programmes.

ICSU has a central Secretariat of 16 staff located in Paris, plus overseas Regional Offices in Africa, Asia and the Pacific, and Latin America and the Caribbean.

The Executive Director reports to the elected Officers and the Executive Board and has overall responsibility for implementing the strategic goals of the organization, managing the Secretariat and overseeing the day-to-day operations of ICSU.

In this capacity, the incumbent will be expected to:
- Act to achieve ICSU's mission, strategy and plans, and contribute to their formulation and development;
- Work with and seek synergy and harmony among all components of the ICSU membership: Scientific Unions, National Members and Interdisciplinary Bodies;
- Ensure effective links between ICSU and partners in the UN and non-governmental sectors and raise funds in support of ICSU's programmes;
- Manage the ICSU Secretariat and its staff in Paris and oversee the Regional Offices around the world.

ICSU is seeking candidates who:
- Have an advanced university degree in science;
- Have at least fifteen years of experience in international collaboration and management of scientific programmes;
- Have leadership as well as strategic, financial and human resources management skills;
- Possess full command of written and spoken English. Working knowledge of French and knowledge of other languages is considered an advantage.

The incumbent should be prepared to conduct frequent world-wide travel. The appointment will start on 1 February 2009 with an initial probationary period of six months.

Further information may be obtained by writing in confidence to the Secretary General at **ED_queries@icsu.org**

Applications with full CV and names of three references should be addressed to the Secretary-General of ICSU at ED_applications@icsu.org by **31 October 2007**. Interviews for short-listed candidates will be arranged in Paris in **February 2008**.

## Director
### McGill and Genome Quebec Innovation Centre

McGill University is seeking a senior scientist to serve as Director of the Innovation Centre sponsored jointly by McGill University and Genome Quebec.

The Innovation Centre is a world class facility dedicated to the fields of genomics and proteomics and their applications to the study of human disease. The Centre operates technology platforms for genotyping and DNA-sequencing along with microarray and proteomic analyses. It also provides a wide range of high quality genomic and proteomic services to academic and commercial clients across North America.

The Director will be a tenured Professor at McGill University and will serve as the chief liaison between the University and Genome Quebec, a major government funding partner in this facility. He or she will be responsible for setting the priorities and future goals of the Centre and, in conjunction with Genome Quebec, for developing financial mechanisms to achieve them. A proven record of success in research and research administration is essential.

The McGill and Genome Quebec Innovation Centre is centrally located on the McGill University campus in downtown Montreal, one of North America's most vibrant and affordable cities. It is adjacent to research facilities belonging to the Faculties of Medicine, Science and Engineering. This research community is one of the most productive and distinguished in North America and opportunities for collaborations and cross-disciplinary research initiatives will be numerous.

Applicants should have an MD, a PhD or the equivalent, and extensive experience in research related to modern genomic and/or proteomic techniques and their applications. A competitive salary commensurate with experience and a start-up package is available, including a Canada Research Chair. Further details on the Canada Research Chairs can be found at www.chairs.gc.ca.

For consideration by the advisory committee, please send a letter outlining your current and future research interests, a copy of your curriculum vitae and the names and addresses of three references to: **Dr. John Robson, Associate Dean for Faculty Affairs, Faculty of Medicine, McGill University, 3605 de la Montagne, Room 220, Montreal, Quebec, Canada, H3G 2M1**. E-mail applications are preferred and should be sent to **facultyaffairs.med@mcgill.ca**. The review of applications will continue until the position is filled.

*All qualified candidates are encouraged to apply: however Canadians and permanent residents of Canada will be given priority. McGill University is committed to equity in employment.*

## Department of Health and Human Services, Food and Drug Administration/Center for Biologics Evaluation and Research, Division of Bacterial, Parasitic and Allergenic Products

# DIRECTOR

The Department of Health and Human Services, Food and Drug Administration, Office of Vaccines Research and Review (OVRR) in the Center for Biologics Evaluation and Research is searching for a Director for the Division of Bacterial, Parasitic & Allergenic Products. The OVRR regulates and performs mission-related research on vaccines and allergenic products to ensure that they are pure, safe and effective. The Director for the Division of Bacterial, Parasitic & Allergenic Products leads a dynamic organization of highly skilled, laboratory-based review scientists and support personnel committed to improving access to vaccines and related products through the development of sound science-based policy, effective regulatory processes and application of quality management principles. Preferred candidates possess specialized knowledge and experience in the development and management of biological programs, as it pertains to evaluating the safety, efficacy and public health significance of vaccines or allergenic biological products; knowledge of the FDA's regulatory and review process; strong leadership and managerial ability; excellent interpersonal skills to deal effectively with interdisciplinary teams and diverse stakeholders; and outstanding oral and written communication skills.

**Qualifications:** Applicants must have a M.D. and/or a Ph.D. in a relevant field, extensive post-doctoral laboratory experience, and a record of publications demonstrating scientific leadership. Candidates for Civil Service or Commissioned Corps appointment and/or for permanent positions must hold US citizenship. The incumbent may also be appointed under Title 42 excepted service. Title 42 209(f) is in the Excepted Service at a salary commensurate with his/her qualifications. Non-US Citizens with permanent residency are required to provide proof with Green Card I-551.

**Salary Range:** $110,363.00-$143,471.00. Physicians may also be eligible for additional salary under the Physician's Comparability Allowance (PCA) up to $30,000 or title 38 compensation.

**Location:** Bethesda, Maryland

**How to Apply:** Submit resume or curriculum vitae with cover letter to: **FDA/CBER, 11400 Rockville Pike, Suite 350, Rockville, MD 20857, HFM-122, Attn: Robin Wilson**, referencing Job Code: **Director, DBPAP**; email to:**recruitment@cber.fda.gov**; or fax to **301-827-1441** or phone **301-827-1400**.

For further information please visit our website at: http://www.fda.gov/cber/inside/vacancy.htm

*DEPARTMENT OF HEALTH AND HUMAN SERVICES IS AN EQUAL OPPORTUNITY EMPLOYER, SMOKE FREE ENVIRONMENT.*



## Evolutionary Biologist, Rank Open

### The School of Environmental and Biological Sciences Rutgers, The State University of New Jersey

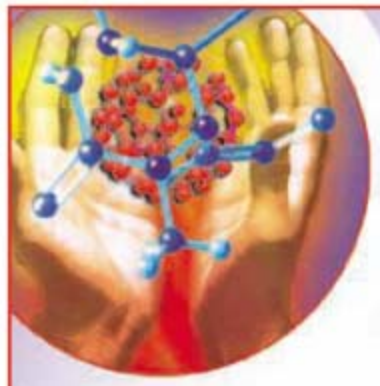
Rutgers University is seeking a scientist with strong research and teaching interests in evolutionary biology, broadly defined. The area of specialization and the faculty rank are open. This faculty position is anticipated to catalyze further growth in evolutionary biology, an effort that involves a number of departments within the University, (e.g., Ecology, Evolution and Natural Resources, Marine and Coastal Sciences, Genetics, and Geology; see **http://evolru.rutgers.edu/ for an overview**). The successful applicant must have a Ph.D., preferably with postdoctoral experience. Senior applicants should have a record of superior research accomplishments and funding. Applicants must have a strong commitment to excellence in both graduate and undergraduate teaching.

The tenure home for this hire will be the Department of Ecology, Evolution and Natural Resources, which is broadly concerned with the structure, function, evolution, and management of natural systems. Research activities involve all levels of organization from the microbial to whole ecosystems on a global scope. Additional information about research and teaching in the department can be viewed on the departmental website (**http://www.rci.rutgers.edu/~deenr/**). In addition to evolution, the department and its allied graduate program (**http://www.rci.rutgers.edu/~deenr/grad/**) have strengths in multiple areas of basic and applied ecology.

**To Apply:** Send cover letter, detailed curriculum vitae, statements describing interests and qualifications in research and teaching, contact information for three references, and up to three selected publications to: **Search Committee – Evolutionary Biologist, Department of Ecology, Evolution, and Natural Resources, Rutgers University, 14 College Farm Road, New Brunswick, NJ 08901-8551**. We strongly encourage the submission of the above material in electronic form (pdf or Word format on CD) addressed to the same address or sent by e-mail to **evosearch@aesop.rutgers.edu**. The committee will begin reviewing applications beginning **November 1, 2007** and will continue until the position is filled. Final appointment is subject to the availability of funds. A September 1, 2008 starting date is anticipated. For additional information, contact **Dr. Lena Struwe**, Search Committee Chair, at **struwe@aesop.rutgers.edu**.

*Rutgers University is an Affirmative Action/Equal Opportunity Employer.*

RUTGERS
THE STATE UNIVERSITY OF NEW JERSEY



# 13 Endowed Professorships

## In Basic Bioscience and Engineering

*The Rensselaer Center for Biotechnology and Interdisciplinary Studies, an outstanding facility for world-class research, is offering up to four endowed positions for exceptional faculty in each of the following focal areas:*

- **Biocatalysis and Metabolic Engineering**
- **Biocomputation and Bioinformatics**
- **Functional Tissue Engineering and Regenerative Medicine**
- **Integrative Systems Biology**

"Constellations" of distinguished professors work collaboratively in each focal area, supported by generous resources to ensure success. We invite you and potential collaborators to put yourselves at the Center of world-class recognition. Appointments and joint appointments will be considered at any level.

RPI is located in Troy, NY, which borders the Hudson River - a short drive to the largest protected state park in the Northeast. Minutes away from the state capital, Troy boasts many of the finest examples of 19th century American Architecture, along with a diverse culture, sporting events and entertainment.

*For the most important research of your life:*

**http://www.rpi.edu/research/constellations/index.html**

To apply send your CV nomination to: **R.E. Palazzo, Acting Provost**
*Bio Constellation Search*
palazr@rpi.edu
Rensselaer Polytechnic Institute, Mailstop: Bio. Tech.- 2nd Floor
110 8th Street , Troy, NY 12180-3590

*Rensselaer Polytechnic Institute is an Affirmative Action/Equal Opportunity Employer.*

Rensselaer
why not change the world?



ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

## Faculty Position in Chemical Engineering

**at Ecole Polytechnique Fédérale de Lausanne (EPFL)**

EPFL anticipates making a faculty appointment at the level of tenure track assistant professor in its Institute of Chemical Sciences and Engineering (ISIC). Outstanding scientists with recognized accomplishments in any field of biochemical engineering will be considered. Exceptional candidates seeking a higher-level appointment may also be considered.

The successful candidate will establish and lead a vigorous, independent research program, interact with existing projects and be committed to excellence in teaching at both the undergraduate and graduate levels. Significant start-up resources and research infrastructure will be available.

Applications including curriculum vitae, publication list, concise statement of research and teaching interests as well as the names and addresses (including email) of at least five references should be submitted in PDF format via the website http://sb.epfl.ch/chemsearch by **October 30, 2007**.

For additional information, please contact **Professor Hubert Girault** (hubert.girault@epfl.ch) or consult the following websites: http://www.epfl.ch/Eplace.html, http://sb.epfl.ch/en and http://isic.epfl.ch

EPFL is an equal opportunity employer.

# Faculty Positions in Cancer Biology

Applications are invited for tenure-track faculty positions in the Cancer Biology and Genetics Program of the Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center. (http://www.mskcc.org/mskcc/html/15422.cfm). Successful candidates will carry out independent research on the genesis, progression, prognosis, prevention and treatment of cancer that synergize with ongoing efforts at the Center. Areas of special interest are, but not limited to: cancer stem cells, tumor microenvironment, tumor angiogenesis, metastasis, cancer genetics, and animal models of cancer.

The new faculty members will join an interactive, interdisciplinary community of scientists and clinicians at the Center, which offers an outstanding basic and translational research environment within expanded state-of-the-art research facilities. Faculty will be eligible to hold graduate school appointments in the Gerstner Sloan-Kettering Graduate School of Biomedical Sciences, the Weill Graduate School of Medical Sciences of Cornell University, as well as the Tri-Institutional MD/PhD Training Program.

**Cancer Biology & Genetics Faculty**
**Robert Benezra, PhD** - Angiogenesis/Differentiation
**Eric Holland, MD/PhD** - Glioma Mouse Models
**Anna Kenney, PhD** - Neural Stem Cells/Brain Tumors
**Robert Klein, PhD** - Cancer Genetics
**Johanna Joyce, PhD** - Tumor Microenvironment
**Joan Massague, PhD** - Cell Regulation/Metastasis
**Harold Varmus, MD** - Molecular Mechanisms of Oncogenesis
**Hans-Guido Wendel, MD** - Genetic Basis for Drug Resistance

Candidates should e-mail their application, preferably in PDF format, to **cancerbio@mskcc.org** by November 1, 2007. The application should include a Curriculum Vitae, a description of past research, a description of proposed research, and copies of three representative publications. Candidates should arrange to have three signed letters of reference sent by email to **cancerbio@mskcc.org** or regular mail to **Joan Massagué, Ph.D, c/o Maria Beckles, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 494, New York, NY, 10021.** The letters should arrive by November 1, 2007. Inquiries may be sent to Maria Beckles at **becklesm@mskcc.org.** EOE/AA.

Memorial Sloan-Kettering Cancer Center
*The Best Cancer Care. Anywhere.*
www.mskcc.org

Sandia National Laboratories
A Department of Energy National Laboratory

## Harry S. Truman Research Fellowship In National Security Science and Engineering

Sandia National Laboratories is one of the country's largest research facilities employing 8,700 people at major facilities in Albuquerque, New Mexico and Livermore, California. Please visit our website at www.sandia.gov.

We are searching for outstanding Ph.D. candidates to apply for the Harry S. Truman Research Fellowship in National Security Science and Engineering. This initial one-year appointment may be extended, at management's discretion, for two additional one-year appointments. The salary is $98,900 per year. This position requires a United States Department of Energy Security Clearance, which requires United States Citizenship.

The Truman Fellowship provides the opportunity for recipients to pursue independent research of their choosing that supports Sandia's national security mission. Candidates are expected to have solved a major scientific or engineering problem in their thesis work or will have provided a new approach or insight to a major problem, as evidenced by a recognized impact in their field.

Candidates must have a Ph.D. within the past 3 years or, will complete all Ph.D. requirements by commencement of appointment, with a broad-based background and extensive knowledge of research in one or more of the following areas: advanced computing, information systems and mathematics; bioscience and technology; combustion, chemical and earth sciences; engineering sciences; geosciences; intelligent systems and robotics; materials science and technology; microelectronics and microsystems; nano sciences and technology; pulsed power and directed energy; and remote sensing and satellite systems. Candidates must be seeking their first national laboratory appointment, have excellent academic and research qualifications, good communication skills, and enjoy working in a team-oriented, dynamic environment.

For complete instructions, please visit:
http://www.sandia.gov/employment/special-prog/truman.
Please submit the complete package to: Roberta Rivera, Sandia National Laboratories, P.O. Box 5800 MS: 1351, Albuquerque, New Mexico 87185-1351, or email rjriver@sandia.gov, or fax 505-845-9802. Please reference Job Requisition Number: 58075. All materials must be received by December 5, 2007.

U.S. Citizenship Required. Equal Opportunity Employer. M/F/D/V.

LOCKHEED MARTIN

# Research Faculty Computational and Systems Biology

The Computational Biology Program at MSKCC (www.cbio.mskcc.org) is seeking innovative investigators for tenure-track positions at the Assistant, Associate, or Full Member level. Pursue basic research, solve biological problems with major emphasis on computational methods and build active bridges to experimental and clinical research. Participate in an innovative expansion of research programs at one of the best clinical-scientific institutions in the world. Work in MSKCC's new Zuckerman Research Center, on Manhattan's Upper East Side, in proximity to Rockefeller University and the medical school of Cornell University. Faculty will be eligible to hold graduate school appointments in the Gerstner Sloan-Kettering Graduate School of Biomedical Sciences, the Weill Graduate School of Medical Sciences of Cornell University, as well as the Tri-Institutional MD/PhD Training Program and Tri-Institutional Computational Biology and Medicine Training Program. Applications are particularly encouraged in:

***Computational Chemical Biology, Pharmacology, Developmental Biology, Neurobiology and Physiology***

Applicants should have a doctoral-level degree and the potential to develop an independent interdisciplinary research program, or a proven record of accomplishments. MSKCC offers a highly interactive, supportive and dynamic research environment with programs in Computational Biology, Developmental Biology, Molecular Pharmacology & Chemistry, Cancer Biology & Genetics, Structural Biology, Immunology, Cell Biology, Molecular Biology, and Human Oncology and Pathogenesis, as well as unparalleled clinical programs in cancer research, treatment and prevention.

E-mail your application (PDF) to **compbio@mskcc.org** preferably by October 1, 2007. Detailed instructions at **www.cbio.mskcc.org/faculty-search/.** Need more information? E-mail **Dwana at: agosto@cbio.mskcc.org. Department Chair: Chris Sander.**

MSKCC is an affirmative action, equal opportunity employer.

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www.mskcc.org

# Yale University
## School of Medicine

### FACULTY POSITION AT THE JUNIOR OR SENIOR LEVEL

### DEPARTMENT OF CELLULAR AND MOLECULAR PHYSIOLOGY

The Department of Cellular and Molecular Physiology seeks applicants for a faculty position at the junior or senior level. Candidates must hold a Ph.D., M.D., or equivalent degree. The candidate's research interest should be in the general area of cellular and molecular physiology with particular emphasis in integrative or translational research and in genetic model systems. Outstanding candidates working in other areas of cellular, molecular, and systems physiology are also encouraged to apply. Excellent opportunities are available for collaborative research, as well as for graduate and medical student teaching.

Applicants should include a curriculum vitae, a statement of research interests and goals, and three letters of reference. Applications should be emailed to leisa.strohmaier@yale.edu in PDF format or sent to:

**Dr. Steven C. Hebert, Chair**
**Department of Cellular and Molecular Physiology**
**Yale University School of Medicine**
**333 Cedar Street**
**P.O. Box 208026**
**New Haven, CT 06510**

Application Deadline: **November 1, 2007**

*Yale University is an Affirmative Action/Equal Opportunity Employer.*

## Sigfried and Janet Weis Center for Research
## Geisinger Clinic
## SCIENTIST FACULTY

**The Weis Center for Research** is seeking outstanding independent scientists for full time positions at ranks equivalent to Assistant, Associate or Full Professor at academic institutions. Substantial resources are available for start-up, ongoing research support and salary. Candidates should have proven records of innovative research at the molecular, cellular or genetic level in areas relevant to human disease. We are particularly interested in candidates with strong programs in signal transduction or cellular neurobiology that complement existing research strengths at the Weis Center (**http://www.geisinger.org/professionals/research/wcr**). Applicants should have a Ph.D. and/or M.D. degree and three or more years of postdoctoral training. Candidates for senior positions are expected to have a history of significant extramural funding. The Weis Center is located on the campus of the Geisinger Medical Center, which is situated in an attractive semi-rural community that affords an outstanding quality of life plus convenient access to major metropolitan areas.

Qualified individuals should submit curriculum vitae, statement of research interests and three reference letters to: **Ms. Kristin Gaul (DJC), Weis Center for Research, Geisinger Clinic, 100 North Academy Avenue, Danville, PA 17822-2600**; or submit via email to **kgaul@geisinger.edu**. Please refer to position **WCR-010228** in the subject line. Applications will be accepted until the position is filled.

*Affirmative Action/Equal Opportunity Employer.*

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Health System

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DANA-FARBER
CANCER INSTITUTE

*Dedicated to Discovery...Committed to Care.*

## ASSISTANT PROFESSOR

(Tenure Track)

### Metabolic Regulation

*The Department of Cancer Biology at Dana-Farber Cancer Institute and the Department of Pathology at Harvard Medical School seek applicants for a tenure-track faculty position. We will consider outstanding applicants interested in any area of cellular and molecular biology, but we are particularly interested in candidates working in the area of regulation of energy homeostasis as it relates to chronic diseases such as cancer, diabetes, aging and neurodegenerative diseases. The ideal candidate will be capable of working at the cell and molecular level, but will also have experience with in vivo model systems. The successful applicant will be expected to develop a strong, independently funded research program and to participate in the teaching mission of the Institute and Harvard Medical School. Candidates must hold a Ph.D. and/or M.D. degree and have a strong record of research accomplishments. Applications from women and minority candidates are encouraged.*

Candidates should submit a curriculum vitae including a full list of publications, a brief statement of previous contributions and future research plans as well as the names and contact information of four references to:

**Faculty Search Committee**
**c/o Deborah Goff**
**Dana-Farber Cancer Institute**
**Room SM1068, 44 Binney Street, Boston, MA 02115**
**E-mail: deborah_goff@dfci.harvard.edu**

HARVARD
MEDICAL SCHOOL

Applications must be received by November 1, 2007

*The Dana-Farber Cancer Institute is an Equal Opportunity Employer.*

**SHARE THE VISION. FIND THE CURE**

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## Cancer Genetics Faculty Positions

The Cancer Biology and Genetics Program of the Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center (http://www.mskcc.org/mskcc/html/15422.cfm), seeks outstanding candidates for tenure-track positions in cancer genetics. Successful candidates will lead independent research programs emphasizing genetic approaches to the genesis, progression, prognosis, prevention and treatment of cancer that synergize with ongoing efforts at the Center. An area of special interest is the identification of genetic determinants of human cancer susceptibility.

The new faculty members will join an interactive, interdisciplinary community of scientists and clinicians at the Center, which offers an outstanding basic and translational research environment within expanded state-of-the-art research facilities. Faculty will be eligible to hold graduate school appointments in the Gerstner Sloan-Kettering Graduate School of Biomedical Sciences, the Weill Graduate School of Medical Sciences of Cornell University, as well as the Tri-Institutional MD/PhD Training Program.

**Cancer Biology & Genetics Faculty**
**Robert Benezra, PhD** - Angiogenesis/Differentiation
**Eric Holland, MD/PhD** - Glioma Mouse Models
**Anna Kenney, PhD** - Neural Stem Cells/Brain Tumors
**Robert Klein, PhD** - Cancer Genetics
**Johanna Joyce, PhD** - Tumor Microenvironment
**Joan Massague, PhD** - Cell Regulation/Metastasis
**Harold Varmus, MD** - Molecular Mechanisms of Oncogenesis
**Hans-Guido Wendel, MD** - Genetic Basis for Drug Resistance

Candidates should e-mail their application, preferably in PDF format, to **cancergen@mskcc.org** by November 1, 2007. The application should include a Curriculum Vitae, a description of past research, a description of proposed research, and copies of three representative publications. Candidates should arrange to have three signed letters of reference sent by email to **cancergen@mskcc.org** or regular mail to **Joan Massagué, Ph.D, c/o Maria Beckles, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 494, New York, NY, 10021.** The letters should arrive by November 1, 2007. Inquiries may be sent to Maria Beckles at **becklesm@mskcc.org.** EOE/AA.

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## Biomedical Science Faculty
## Washington State University Spokane
## Program in
## Basic Medical Education – WWAMI

Applications are sought for up to four tenure-track faculty positions for the new WWAMI (Washington, Wyoming, Alaska, Montana, Idaho) Medical Education Program at Washington State University (WSU)-Spokane. These positions will be at the Assistant/Associate professor level, and will also be eligible to receive an affiliate faculty, non-tenure track appointment at the University of Washington School of Medicine.

Successful candidates will be expected to develop a strong, federally funded biomedical research program, as well as teach in one of the first year medical school courses. Preference will be given to those applicants with research interests in one of the existing areas of strength, including chromosome biology/DNA repair/epi-genetics, cancer biology, sleep and performance, substance abuse and addiction, reproductive biology, at risk families and children and translational and clinical research. Strong collaborative ties exist with the WSU Pullman campus. Further details about these positions including qualifications requirements may be found at the website **www.chr.wsu.edu**.

Further information about the WWAMI Program please see: **http://www.spokane.wsu.edu/academics/Health_Sciences/WWAMI**

Review of applications will begin **October 1, 2007**.

*EEO/AA*

## POSITIONS OPEN

The Department of Chemistry and Biochemistry at Denison University invites applications for a tenure-track position at the **ASSISTANT PROFESSOR** level in organic chemistry, starting fall 2008. Successful candidates will demonstrate a strong commitment to teaching at the undergraduate level and the capacity to develop a productive research program that involves undergraduates. Preference will be given to candidates whose research interests expand the diversity of research opportunities available to our students. Teaching responsibilities will include general and organic chemistry and an advanced organic synthesis/mechanism course. Our American Chemical Society-accredited Department has well-developed programs in both chemistry and biochemistry, excellent classroom and laboratory facilities, extensive computer resources, and a broad range of instrumentation that is used in both teaching and research: spectroscopy (400 megahertz nuclear magnetic resonance, Fourier transform infrared, ultra-violet-visible spectroscopy, AA, microplate absorbance/fluorescence/luminescence), separations (gas chromatography [GC]/mass spectometry and other GC methods, high performance liquid chromatography, electrophoresis, centrifugation), electrochemistry, and imaging (multiwavelength digital imaging, scanning probe microscopy).

A Ph.D. is required and postdoctoral experience is preferred. Applicants should submit a cover letter, curriculum vitae including a publication list, undergraduate and graduate transcripts, a statement of teaching philosophy, and a summary of research plans. These materials and three letters of recommendation should be sent to: **Dr. Peter Kuhlman, Department of Chemistry and Biochemistry, Ebaugh Laboratories, Denison University, Granville, OH 43023.** Electronic submissions (Adobe PDF format only) may be sent via **e-mail: kuhlman@denison.edu.** Denison University is located in central Ohio, 30 minutes east of Columbus and about 2.5 hours from Cleveland, Cincinnati and Pittsburgh, Pennsylvania. For full position description, see **website: http://www.denison.edu/chem/orgposn/.** To assure full consideration, completed applications must be received by October 15, 2007. *Denison University is an Equal Opportunity and Affirmative Action Employer. In a continuing effort to diversify our campus community, women and people of color are strongly encouraged to apply.*

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### FACULTY POSITION VIROLOGIST

The College of William and Mary invites applications for a tenure-track position at the **ASSISTANT PROFESSOR** level in virology with an anticipated start date of August 2008. Desirable areas of expertise include, but are not limited to, classical and molecular virology, viral genetics, marine virology, viral evolution and/or ecology, and plant virology. Applicants should consider whether their research is appropriate for work in a primarily undergraduate institution, with biosafety levels not to exceed BSL-2. Candidates must display scientific breadth and demonstrate the potential and motivation to achieve excellence in teaching in a broadly based Biology Department. Candidates must also maintain an active research program with both undergraduate and Master's-level students, and obtain external funding to support their research. Competitive startup funds will be provided. Previous teaching experience will be advantageous, and postdoctoral experience is expected. Teaching responsibilities will include one upper-level virology course with a laboratory for one semester, and another course for the second semester, to be negotiated with the Chair. Review begins on November 1, 2007, and will continue until the appointment is made. For full consideration, submit a letter of application, curriculum vitae, statements of research interests and teaching philosophy, and the names and contact information for three references, through the College's online recruitment system at **website: http://jobs.wm.edu.** *The College of William and Mary is an Equal Opportunity/Affirmative Action University. Members of underrepresented groups (including people of color, persons with disabilities, Vietnam veterans, and women) are encouraged to apply.*

## POSITIONS OPEN

### VICE PRESIDENT and DEAN of ACADEMIC AFFAIRS
**The New England College of Optometry**

The New England College of Optometry invites nominations and applications for the position of Vice President and Dean of Academic Affairs. The successful candidate serves as the Institution's chief academic officer with responsibilities that include the management, development, and implementation of all academic degree programs and reports to the President of the College.

The ideal candidate must be an effective leader and excellent communicator, with the drive and imagination to explore new approaches to the education of optometry students. Required qualifications include a strong track record of administrative experience in an academic setting, a doctoral-level degree (O.D. preferred), and a demonstrated capacity to lead and work effectively with faculty, students, clinicians, and business leaders.

Applicants should submit a letter of interest, complete curriculum vitae, and the names and complete contact information for three references by October 15, 2007.

The College, founded in 1894 and located in the Back Bay of Boston, currently enrolls approximately 450 students in our O.D., M.S. in vision science, and international programs, and employs nearly 50 full-time faculty members. The school is recognized as a leader in innovative optometric education, research, and community-based eye care.

Starting date: July 1, 2008.

Confidential inquiries, nominations, and application materials should be directed to:

**Steven B. Koevary, Ph.D.**
**Search Committee Chair**
**The New England College of Optometry**
**424 Beacon Street**
**Boston, MA 02115**
**Telephone: 617-266-2030, extension 5259**
**E-mail: koevarys@neco.edu**
**Website: http://www.neco.edu**

*The New England College of Optometry is an Affirmative Action, Equal Opportunity Employer.*

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### FACULTY POSITIONS
**Membrane, Cell, and Tissue Morphogenesis**
**Carnegie Mellon University**

The Department of Biological Sciences at Carnegie Mellon University seeks to fill two **TENURE-TRACK** positions studying the molecular mechanisms of membrane, cell, and tissue morphogenesis, with special emphasis on model systems and neuroscience. Carnegie Mellon has a long history of interdisciplinary research with strengths in light microscopy, fluorescent reagent development, magnetic imaging and computation. Research programs of current faculty include the areas of cell/developmental biology, genetics/molecular biology and biochemistry/biophysics, computational biology and neuroscience (see departmental **website: http://www.cmu.edu/bio).** Successful candidates will be expected to develop strong, innovative research programs and to participate in the undergraduate and graduate educational programs. Candidates must have a doctoral degree and strong research credentials.

Please send curriculum vitae, a statement of research interests, and three letters of recommendation to: **Dr. Jonathan Minden, Department of Biological Sciences, Carnegie Mellon University, 4400 Fifth Avenue, Pittsburgh, PA 15213.** Review of applications will begin November 1, 2007. *Carnegie Mellon University is an Equal Opportunity/Affirmative Action Employer. Women, minorities, veterans, and disabled persons are encouraged to apply.*

## POSITIONS OPEN

The Department of Psychology at the University of Pittsburgh announces a tenure-track position at the **ASSISTANT or ASSOCIATE PROFESSOR** level (pending budgetary approval) in the genetics of human behavior.

Candidates for this position should exploit genetic approaches in a biologically informed research program targeted towards understanding associations among genes, brain, and behavior. Investigators pursuing research on measured genetic variation or gene expression are encouraged to apply and applications in quantitative behavioral genetics will be considered as well. The area of specialization should fall within the scope of one or more of our graduate training areas in biological and health, clinical, cognitive/cognitive neuroscience, developmental, or social psychology. For more information about these specialty areas and existing programs of faculty research, see **website: http://www.pitt.edu/~psych.**

The University has a broad range of outstanding resources and established collaborations that facilitate research in genetics and neuroscience, including those involving the Department of Human Genetics **(website: http://www.hgen.pitt.edu),** Center for the Neural Basis of Cognition **(website: http://www.cnbc.cmu.edu),** the Center for Neuroscience at the University of Pittsburgh **(website: http://cnup.neurobio.pitt.edu),** and the Department of Psychiatry **(website: http://www.wpic.pitt.edu).**

The review of applications will begin immediately, with applications received by November 1, 2007, receiving full consideration. Interested parties should submit a cover letter, a research and teaching statement, three letters of recommendation, representative publications, and curriculum vitae to: **Genetics Search, Department of Psychology, University of Pittsburgh, 210 South Bouquet Street, 3129 Sennott Square, Pittsburgh PA 15260.** For more information about the position, please contact **Anthony Caggiula** at **telephone: 412-624-4501 (e-mail: tonypsy@pitt.edu).**

*The University of Pittsburgh is an Affirmative Action, Equal Opportunity Employer. Women and members of minority groups underrepresented in academia are especially encouraged to apply.*

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University of Wisconsin, Oshkosh, seeks tenure-track **ASSISTANT PROFESSOR in BIOLOGY** with specialty in animal cell physiology, beginning September 1, 2008. Ph.D. required; postdoctoral and teaching experience desirable. Responsibilities: share in teaching courses in molecular and cell biology, animal and human physiology, introductory biology; develop a research program in cell physiology; pursue extramural funding; supervise M.S. theses. Send letter of application, brief statements of teaching philosophy and research interests, curriculum vitae, reprints, three current letters of recommendation, and transcripts (official or photocopy) to: **Chair, Department of Biology and Microbiology, University of Wisconsin Oshkosh, Oshkosh, WI 54901.** Deadline: January 3, 2008. At least one letter of recommendation should come from the candidate's current institution. For additional information, see the departmental web page at **website: http://www.uwosh.edu/departments/biology/.** *Employment will require a criminal background check. Affirmative Action/Equal Opportunity Employer.*

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### PLANT PHYSIOLOGIST

The Sonoma State University Biology Department seeks a dynamic Teacher-Scholar for a tenure-track **ASSISTANT PROFESSOR** position starting fall 2008. We are especially interested in a broadly trained Plant Physiologist whose research focuses on mechanisms of adaptation to environmental stress and/or change. The successful candidate will be expected to maintain an externally funded research program involving both undergraduate and graduate students and teach in his/her areas of expertise. Review of completed applications will begin October 1, 2007. See full job announcement at our **website: http://www.sonoma.edu/biology.**

## POSITIONS OPEN

### GENETICS and PHYSIOLOGY POSITIONS

The Department of Biology at Creighton University invites applications for two tenure-track, **ASSISTANT PROFESSORSHIPS** in (1) genetics and (2) physiology to begin August 2008. Candidates should be qualified to teach genetics with laboratory or physiology with laboratory and a semester course in general biology (cellular or organismal level), in addition to other biology courses in their respective disciplines for introductory, upper-division and/or nonscience undergraduates. Ph.D. required; postdoctoral experience preferred. Candidates should possess a strong desire to teach in a liberal arts environment. Candidates should have a research program in any area within the discipline, amenable to the mentoring of undergraduate research students. Graduate student mentoring is possible through affiliated programs. Normal teaching load is three preparations per semester (for example, two lecture courses, one with laboratory). Tenure and advancement require excellent teaching and development of a sustainable research program leading to peer-reviewed publications. Opportunities exist for research collaboration with faculty in other departments, including those in Creighton's health sciences schools. Additional information on these positions, the Department and the University is available at **website: http://biology.creighton.edu/jobs/.** To apply, send (1) curriculum vitae; (2) statements of teaching philosophy, research interests and skills, and long-term goals; (3) documentation (if available) of teaching effectiveness; (4) undergraduate and graduate transcripts; and (5) three letters of reference to: **Department of Biology, Creighton University, Omaha, NE 68178-0103, Attention Dr. Charles Brockhouse (Chair, Genetics Search Committee),** or **Dr. John Schalles (Chair, Physiology Search Committee).** Application review will begin October 1, 2007, and continue until the positions are filled. *Creighton is a Catholic Jesuit institution that seeks qualified applicants from all backgrounds who believe they can contribute to the University's outstanding educational traditions. We are an Equal Opportunity Employer/Affirmative Action Employer. Women and minority candidates are strongly encouraged to apply.*

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### PLANT or ECOSYSTEMS ECOLOGIST
**Colgate University**

The Department of Biology seeks a tenure-track **ASSISTANT PROFESSOR** to start August 2008. Ph.D. or expectation of completion this academic year required; teaching and postdoctoral research experience desirable. The successful candidate will: contribute to a foundation course entitled Evolution, Ecology, and Diversity; teach elective courses in plant ecology and in their area of specialty; and contribute to interdisciplinary and University-wide programs (including environmental studies). The appointee will join a biology faculty deeply committed to a strong, research-oriented program involving undergraduate students and will add to this effort by offering a research tutorial in their area of interest. The Department offers excellent teaching and research facilities, including a new greenhouse and access to diverse local field sites. Please forward a letter of application with curriculum vitae, transcripts, and separate statements of teaching philosophy and research interests to: **Dr. Timothy McCay, Chair Ecology Search, Department of Biology, Colgate University, Hamilton, NY 13346-1398,** and also arrange to have three letters of recommendation sent to this address. Review of applications will begin October 16, 2007, and continue until the position is filled. We intend to begin interviewing candidates by the beginning of November. Applicants with dual-career considerations can find postings of other employment opportunities at Colgate and at other institutions of higher education in upstate New York at **website: http://www.upstatenyherc.org.** *Colgate University is an Equal Opportunity/Affirmative Action Employer. Developing a diverse faculty and staff furthers the University's academic mission for our increasingly diverse student body.*

## POSITIONS OPEN

50th ANNIVERSARY Florida Institute of Technology
High Tech with a Human Touch

### HEAD, BIOLOGICAL SCIENCES
**Florida Institute of Technology**

The Department of Biological Sciences at the Florida Institute of Technology seeks an individual with significant accomplishments in teaching, research productivity, and grants acquisition for the position of Department Head. Florida Tech is an independent university committed to the pursuit of excellence in teaching and research in the sciences and engineering. Over 3,300 students are enrolled on the Melbourne campus located in a space and high-technology center on Florida's east coast, with a semitropical climate. Biological Sciences is a flagship academic unit in the College of Sciences with strong B.S., M.S., and Ph.D. degree programs in the areas of marine biology, ecology, and cell/molecular biology. There are currently 17 full-time faculty members, 63 graduate students, and 350 undergraduate students. For more information please visit **website: http://www.fit.edu/biology.** Successful candidates must have a Ph.D. degree in a biological science, exceptional communication skills, a clear vision for the future of the Department, and experience in planning, budgeting, and operational management of research projects. The area of specialization of the candidate is open. Applicants should send a letter of application, curriculum vitae, statement of educational and administrative philosophy, and names and contact information of four references to **e-mail:-bioheadsearch@fit.edu.** Alternatively, materials may be sent to:

**Dr. Michael Babich**
**Biology Head Search Committee**
**Florida Institute of Technology**
**150 W. University Boulevard**
**Melbourne, FL 32901**

Review of applications will begin October 15, 2007. *Florida Institute of Technology is an Equal Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply.*

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The Amherst College Department of Chemistry (**website: http://www.amherst.edu/~chemistry/**) invites applications for a full-time tenure-track **ASSISTANT PROFESSORSHIP** in biochemistry or bio-organic chemistry beginning in July 2008. The position requires a Ph.D., and calls for teaching at the introductory and advanced undergraduate levels. Opportunities for teaching in interdisciplinary courses and programs are also available. The successful candidate will be expected to establish a vigorous research program in which undergraduates can substantively participate. The research program may span the boundaries between biochemistry and other sciences. Applicants should submit curriculum vitae, undergraduate and graduate transcripts, a statement of teaching philosophy, and a detailed description of their research plans, and should arrange for the forwarding of three letters of reference, all to: **Professor Joseph N. Kushick, Chair, Department of Chemistry, Amherst College, Amherst, MA 01002.** Review of materials will begin October 8, 2007.

Amherst College is a private, liberal arts institution of some 1,600 students and 190 faculty. Located in the Connecticut River Valley of western Massachusetts, it participates with Hampshire, Mount Holyoke, and Smith Colleges, and the University of Massachusetts in the Five-College Consortium. The College enrolls students from nearly every state and from more than forty countries.

*Amherst College is an Equal Opportunity, Affirmative Action Employer and encourages women, persons of color, and persons with disabilities to apply. The administration, faculty, and student body are committed to attracting qualified candidates from groups currently underrepresented on campus.*

## POSITIONS OPEN

### CHAIR of BIOLOGICAL SCIENCES
**Michigan Technological University**

The Department of Biological Sciences at Michigan Technological University invites applications for the position of Chair to begin in the 2008-2009 academic year. The Chair will be responsible for managing the academic and financial affairs of the Department, the development and growth of our undergraduate and graduate programs, and resource development. The Chair is expected to maintain a dynamic research program compatible with existing departmental strengths in biochemistry and molecular biology, ecology and limnology, and the health sciences. The successful candidate will have achieved the academic rank of **ASSOCIATE or FULL PROFESSOR,** and possess a distinguished record of research, teaching, and procurement of extramural funding.

We seek an individual with the vision and skills to elevate the Department's prominence in biological research, further our strong tradition of educational excellence, and grow our M.S. and Ph.D. programs. The Chair is expected to foster collaborations with other departments, centers, and institutions; and advance the Department's position as a key player in life science initiatives such as sustainability and biotechnology.

Review of applications will begin September 24, 2007, and continue until the position is filled. For a broader position description see **website: http://www.bio.mtu.edu/chair.htm.** Please contact **Casey Huckins (telephone: 906-487-2475; e-mail: cjhuckin@mtu.edu)** if you have questions about this position. Applicants should send: a letter of interest; curriculum vitae; statements of research, teaching, and administrative philosophies; and names of four references to:

**Dr. Casey Huckins, Search Committee Chair**
**Department of Biological Sciences**
**Michigan Technological University**
**1400 Townsend Drive**
**Houghton, MI 49931**

*Michigan Technological University is an Equal Opportunity Educational Institution/Equal Opportunity Employer/Affirmative Action Employer.*

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### OPTICAL IMAGING SCIENTIST

The Department of Medicine/Section of Cardiology is seeking qualified applicants for a full-time **RESEARCH ASSOCIATE (ASSISTANT/ASSOCIATE/PROFESSOR)** position to work with **Dr. Stephen Archer** on studies of basic mechanism of oxygen sensing and experimental therapies for pulmonary hypertension. The successful applicant will join a new Vascular Biology Research Group, led by Dr. Archer.

The primary activity of the Research Associate (Assistantt/Associate/Professor) is academic research, along with development of and management of an optical imaging core in association with a faculty member or team. Qualified applicants are required to possess a doctorate degree in a relevant discipline (e.g. biochemistry or pharmacology). Applicants should possess excellent knowledge and have a demonstrated track record of expertise performing experiments using multiphoton confocal microscopy technology. Expertise in patch clamping, and cellular electrophysiology is preferred. Three to five years of postdoctoral training is required. A demonstrated track record of publication and the potential to apply for peer reviewed funding is preferred. Responsibilities include data management, analysis, manuscript preparation, and submission of protocols for approval by the Institutional Animal Care and Use Committee. Preference will be given to applicants who have experience at the University of Chicago. Compensation and level of appointment are dependent on qualifications. The University provides a generous package of fringe benefits. Interested applicants should submit cover letter, curriculum vitae and three letters of reference via e-mail to **Dr. Stephen Archer, e-mail: sarcher@medicine.bsd.uchicago.edu.** *The University of Chicago is an Affirmative Action/Equal Opportunity Employer.*

## The Program in Science Technology and Environmental Policy at Princeton University 2008-2009
## Fellowship Program for Distinguished Faculty, Senior Scholars, and Practitioners

The Program in Science, Technology and Environmental Policy (**STEP**) at Princeton University's Woodrow Wilson School of Public and International Affairs (Michael Oppenheimer, director) announces its 2008-2009 Senior Fellowship program. STEP will award fellowships accompanied by one-half year support at full salary or full year at half salary to eligible, distinguished faculty, scholars and practitioners. These awards are designed to promote advanced policy research in any of these areas: global climate change, global environmental governance, energy policy, air pollution, conservation biology and ecology, bioethics and biotechnology, environmental health and disease, environmental economics, science and security policy, and information security. We seek candidates whose interests complement those of STEP faculty. Outstanding faculty, independent scholars, and practitioners anywhere in the world are eligible to apply. The fellows program is open to all regardless of citizenship.

STEP fellows will have the opportunity to interact and collaborate with STEP faculty, other fellows, researchers and students and to participate in the various activities of the STEP program including faculty graduate seminars, colloquia, and public lectures. As part of the fellowship experience, STEP fellows will be involved in some of the following activities: participation on a university sponsored research project, collaboration with STEP faculty on projects of mutual interest, attendance at STEP seminars, and participation in meetings with STEP students, faculty, and postdocs.

Salaries vary according to individual circumstances, but will not exceed a maximum that is set each fall. Rank is contingent upon qualifications. Applicants not on leave from other positions will be eligible for employee benefits; others will be eligible for health insurance only. Applicants interested in teaching a seminar at Princeton University during their visit should so indicate.

Applicants should send a CV and cover letter (no more than 1,000 words) describing their proposed activities while at Princeton. On a separate sheet of paper, applicants should submit a confidential statement indicating (1) their salaries (not including summer research support) for the current academic year and (2) financial support available to them from their home institutions, other grantors, and any other sources during their time at Princeton. Send all materials via email to **Charles Crosby** at **ccrosby@princeton.edu**. The review process will begin immediately and continue until positions are filled.

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## Program in Science Technology and Environmental Policy at Princeton University - 2008-2009 Postdoctoral Fellowship Program

The Program in Science, Technology and Environmental Policy (**STEP**) at Princeton University's Woodrow Wilson School of Public and International Affairs (Michael Oppenheimer, Director) announces its 2008-2009 Postdoctoral Fellowship Program. STEP will award one-year research positions (with the possibility of renewal for a second year) to eligible, talented researchers. These awards are designed to promote basic policy-relevant research under the supervision of one or more STEP faculty members in the broad areas of global climate change, air pollution, energy policy, global environmental governance, conservation biology and ecology, bioethics and biotechnology, environmental health and disease, environmental economics, science and security policy, and information security. The Postdoctoral Fellows Program is open to all regardless of citizenship, but requires a completed doctorate and does not support work towards the completion of a degree. STEP fellows will be eligible for salary and full employee benefits in accordance with University guidelines.

Applicants should send a CV and a cover letter describing their areas of expertise and interest via email to **Charles Crosby** at **ccrosby@princeton.edu**. The review process will commence immediately and continue until positions are filled.

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For more information about applying to Princeton please link to:
**http://web.princeton.edu/sites/dof/ApplicantsInfo.htm**

Candidates may choose to complete the "Invitation to Self-Identify" form **http://web.princeton.edu/sites/dof/forms/PSoftSelfID.pdf**. Providing the self-identification information is completely voluntary and declining to submit the information will not adversely affect your candidacy.

*Princeton University is an Equal Opportunity/ Affirmative Action Employer.*

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**UNIVERSITY of LIMERICK**
OLLSCOIL LUIMNIGH

*The University of Limerick (UL) with over 11,500 students and 1,200 staff is a young, energetic and enterprising university with a proud record of innovation in education and excellence in research and scholarship. UL is situated on a superb riverside campus of over 300 acres with the River Shannon as a unifying focal point. Outstanding recreational, cultural and sporting facilities further enhance this exceptional learning and working environment.*

## Research Professor in Membrane Structural and Functional Biology

The University of Limerick has a strategic commitment to the area of structural biology with a particular emphasis on cellular membranes and on structure determination by crystallographic and spectroscopic means. Several groups at the University of Limerick share an interest in membrane structural and functional biology. A leading Centre for Membrane Structural and Functional Biology is being developed which will support world-class research. This Centre will enhance the Irish economy in a sustainable way by contributing to the knowledge base in membrane biology, drug discovery and sensor development.

The University now wishes to appoint an outstanding individual as a Research Professor in Membrane Structural and Functional Biology. The candidate should have extensive expertise in membrane structural and functional biology and be interested in collaboration with other groups at the University. The candidate should have an outstanding record of publication, obtaining research funding and a track record in innovation.

**Salary Scale €109,106 - €140,385 p.a.**

Informal enquires may be made to:

**Professor Vincent Cunnane, Vice President Research, University of Limerick, Ireland.**
**Telephone: +353 61 202686**
**Email: Vincent.Cunnane@ul.ie**

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Further information for applicants and application material is available from: **Human Resources – Email: hr@ul.ie – Web: http://www.ul.ie/hrvacancies/**

Please note your application must include:

A letter/email of introduction indicating how you meet the criteria outlined in the advertisement and/ or information for applicants.

A completed University of Limerick Application Form.

The closing date for receipt of applications is **Wednesday 31st October 2007**. Applications must be submitted to the HR Division using the appropriate University Application Form before **12 noon** on the closing date.

**Applications are welcome from suitably qualified female and male candidates. The University is an equal opportunities employer and committed to selection on merit.**

NDP
National Development Plan 2007 - 2013

www.ul.ie

## POSITIONS OPEN

**BIOCHEMIST or BIO-ORGANIC CHEMIST.** The Chemistry Department at the University of Alabama in Huntsville invites applications for a tenure-track position at the **ASSISTANT** or **ASSOCIATE PROFESSOR** level to begin August 2008. Applicants must have a Ph.D. in chemistry or a related discipline with postdoctoral experience. The successful candidate should have a strong commitment to maintain an externally funded research program in biochemistry and/or bio-organic chemistry with graduate students in chemistry as well as interdisciplinary biotechnology or materials science Ph.D. programs. Teaching duties at the undergraduate and graduate level include biochemistry, organic chemistry, or general chemistry, as well as courses in the candidate's area of interest. Ideally, the candidate's research interests should complement those of the current faculty in the biotechnology and materials science programs and utilize existing facilities in structural biology, materials characterization, and molecular modeling. Facilities include an 800 megahertz nuclear magnetic resonance (NMR) spectrometer dedicated to biomolecular NMR, Rigaku, Bruker and X-ray diffraction equipment, access to the Southeast Regional Collaborative Access Team beamlines at Argonne National Laboratory, scanning probe microscopy and scanning electron microscopy systems, Kratos XPS/Auger spectrometer, and Itanium 2 and Dell Beowulf clusters. The UAH campus is located in Huntsville, Alabama which is also home to the nation's second largest research park, NASA's Marshall Space Flight Center, and the newly formed Hudson Alpha Institute for Biotechnology. Applicants are requested to submit curriculum vitae; a proposed research plan with estimated startup needs; a statement of teaching interests and experience; and the names and contact information of at least three references to **John Shriver, Chair of the Faculty Search Committee,** via **e-mail: biops@uah.edu.** The deadline for application is November 1, 2007. Further information about the Department is found at **website: http://chemistry.uah.edu/.** *Applications from women and minority candidates are especially encouraged. The University of Alabama in Huntsville is an Equal Opportunity/Affirmative Action Employer.*

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**FACULTY POSITION**
**Institute of Molecular and Cellular Biology**
**National Taiwan University**

The Institute is seeking an outstanding individual to fill a full-time Faculty Position available on August 1, 2008. The level of appointment is open. The specific research area should be related to molecular and/or cellular biology. Candidates must have a Ph.D. degree and have a postdoctoral experience. Preference will be given to individuals who submit curriculum vitae, a brief statement of research and teaching course(s), and three recommendation letters prior to December 15, 2007, to: **Chair, Faculty Search Committee, Institute of Molecular and Cellular Biology, National Taiwan University, Number 1, Section 4, Roosevelt Road, Taipei, Taiwan 10617. Website: http://cell.lifescience.ntu.edu.tw/english/index.htm.**

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**The UCLA School of Public Health (SPH). TENURE-TRACK FACULTY POSITION** in the field of global climate change. Potential disciplinary areas for this appointment are on the SPH **website: http://www.ph.ucla.edu/pdfs/job_post_08152007.pdf.** Candidates must have an earned Doctorate with experience and scholarship in the area of climate change. Applications will be considered beginning December 3, 2007, until position filled. Faculty appointment level and salary will be determined based on candidate's experience and qualifications. Please send curriculum vitae and letter of interest to: **Ms. Susan Fisher, Coordinator, Climate Change Search, UCLA School of Public Health, P.O. Box 951772, Los Angeles, CA 90095-1772.** *UCLA is an Affirmative Action/Equal Opportunity Employer. Women and underrepresented minorities are encouraged to apply.*

## POSITIONS OPEN

**OREGON HEALTH & SCIENCES UNIVERSITY**

The Oregon Health & Sciences University (OHSU) Department of Behavioral Neuroscience invites applications for a **TENURE-TRACK JUNIOR FACULTY POSITION.** We seek an outstanding applicant with a Ph.D. or equivalent degree, postdoctoral experience, and a strong publication record. Evidence of extramural research funding is desirable. The position is not limited in area of expertise; however, special consideration will be given to individuals with interests in the area of alcohol and drug abuse. Individuals with expertise in any area of genomics, including human genetics, are especially encouraged to apply. *The successful applicant must be a U.S. citizen or permanent resident.* OHSU places a high priority on cultural diversity; thus, we seek candidates with a demonstrated sensitivity to and understanding of the diverse academic, socioeconomic, cultural, disabled and ethnic backgrounds of OHSU's students and employees. The salary and startup package is very competitive. The review of applications will begin in September 2007. The position will remain open until filled. Send cover letter, curriculum vitae, statement of research interests, and contact information for three references to: **Rebecca Salzer (e-mail: salzerr@ohsu.edu), Department Administrator, Oregon Health & Science University, Department of Behavioral Neuroscience, L-470, 3181 S.W. Sam Jackson Park Road, Portland, OR 97239-3098. Website: http://www.ohsu.edu/behneuro/.**

*OHSU is an Affirmative Action, Equal Opportunity Employer. Women, minorities, disabled persons, Vietnam era and disabled veterans are encouraged to apply. OHSU is a smoke-free workplace.*

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**MASSACHUSETTS INSTITUTE of TECHNOLOGY**
**Department of Chemistry**

The Massachusetts Institute of Technology Department of Chemistry invites applications for tenure-track appointments beginning July 2008. Applicants with teaching and research interests in biological, organic, inorganic and physical chemistry are encouraged to apply. The appointments will be at the rank of **ASSISTANT PROFESSOR,** but outstanding senior applicants could be considered.

A completed application will include curriculum vitae, a one-page summary of research plans, two or more research proposals, and three letters of recommendation. Application instructions will be posted by September 3, 2007, on MIT Chemistry's **website: http://web.mit.edu/chemistry/www/index.html.** To receive full consideration, completed applications must be received by October 1, 2007.

*MIT is an Equal Opportunity/Affirmative Action Employer. Applications from women, minorities, veterans, older workers, and individuals with disabilities are strongly encouraged.*

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**FORMULATION CHEMIST** needed with two years of experience to develop formulation of new drugs that are bioavailable efficacious and stable. Prepare stability protocols. Prepare and review standard operating procedures (SOPs). Optimize and scale up manufacturing processes. Install, validate (installation qualification/operational qualification) and maintain pharmaceutical equipment under current good manufacturing practice. Use capsule filler, tablet press, hi-shear granulator, fluid bed dryer, tablet coater, disintegration tester, friability tester, blender, extruder and other process related equipments. Mail resume to: **QS Pharma, 3 Chelsea Parkway, Suite 305, Broothwyn, PA 19061.** Job location: Boothwyn, Pennsylvania.

## POSITIONS OPEN

**FACULTY POSITIONS**
**Marine Ecology, Comparative Animal Physiology, and Structural Biology**
**San Diego State University**

The Department of Biology seeks to fill three faculty positions at the **ASSISTANT PROFESSOR** level. Successful applicants will be expected to develop and maintain a vigorous, externally funded research program that complements the Department's current Programs in Cell and Molecular Biology, in Ecology, and in Evolutionary Biology. Our faculty participates in our undergraduate and graduate (M.S. and Ph.D.) teaching programs, and have the ability to interact with and mentor a diverse student body. Candidates with research interests in the following areas are desired: (a) marine ecology, working in coastal or estuarine system studying processes at the population, community, or ecosystem level; (b) comparative animal physiology/functional biology, with research interests centering on addressing evolutionary and/or ecological questions in whole animal physiology/functional biology using modern comparative/phylogenetic approaches; (c) structural biology with preference for candidates employing state-of-the-art techniques of cryo-electron microscopy, X-ray diffraction, and/or multidimensional nuclear magnetic resonance to study the structure of biological macromolecules, macromolecular assemblies, and/or subcellular organelles.

The Department of Biology houses newly renovated facilities that include the San Diego State University Electron Microscope Facility, Microchemical Core Facility, Ecology Analytical Laboratory, the recently opened Coastal Waters Laboratory, and three biological field stations occupying over 6,000 acres of diverse habitats. Applicants should submit curriculum vitae, separate statements of research and teaching interests, three representative publications, and arrange for three letters of recommendation to be sent to either the: **Marine Ecology, Animal Physiology, or the Structural Biology Search Committee, Department of Biology, San Diego State University, San Diego, CA 92182-4614.** Review of applications will begin on October 8, 2007, and will continue until the positions are filled. For more information see **website: http://www.bio.sdsu.edu/jobs.**

*SDSU is a Title IX, Equal Opportunity Employer and does not discriminate against individuals on the basis of race, religion, national origin, sexual orientation, gender, marital status, age, disability or veteran status, including veterans of the Vietnam era.*

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**ASSISTANT/ASSOCIATE PROFESSOR**
**RNAi in Gene Regulation and Small RNAs as Biopharmaceutical Agents**

The Center for Pharmaceutical Biotechnology and the Department of Biopharmaceutical Sciences, University of Illinois at Chicago, invite applications for a tenure-track faculty position at the level of **ASSISTANT or ASSOCIATE PROFESSOR** in a general area of RNAi-based gene regulation and/or small RNAs as biopharmaceutical agents. Responsibilities include developing a strong, externally funded research program and teaching in graduate and professional programs. The successful candidate will have joint appointments in the Center for Pharmaceutical Biotechnology and the Department of Biopharmaceutical Sciences. Ph.D. and at least one year of postdoctoral experience in areas related to biology of RNAi and/or small RNAs are required. Candidates at the Assistant Professor level must have strong potential for attracting extramural funding; candidates at the Associate Professor level must have a strong record of successful extramural funding. Position available spring 2008. For fullest consideration, send curriculum vitae, description of research interests and three letters of reference by October 15, 2007, to **e-mail: cpbhr@uic.edu** or **Dr. Alexander Mankin, RNA Search Committee, Center for Pharmaceutical Biotechnology, M/C 870, University of Illinois at Chicago, 900 S. Ashland Avenue, 3052 MBRB, Chicago, IL 60607-7173** (electronic applications encouraged). *UIC is an Affirmative Action/Equal Opportunity Employer.*

Penn
University of Pennsylvania

## FACULTY POSITION IN NEUROBIOLOGY

The Biology Department of the University of Pennsylvania invites applicants for a tenure track position in the area of Neurobiology, with a focus on individuals whose research spans from genes to brain to behavior. We anticipate that this appointment will be made at the Assistant Professor level, but outstanding senior candidates will be given serious consideration. We are particularly interested in individuals carrying out mechanistic studies aimed at defining the role of specific genetic networks or neural circuits in behavior. Suitable experimental approaches include genetics, biophysics, cellular imaging, functional imaging, electrophysiology, and molecular biology. We would welcome applications from researchers working on mammalian systems or on genetically tractable model systems such as zebrafish, *D. melanogaster*, and *C. elegans*. Candidates are expected to have demonstrated excellence and productivity in research and to participate in undergraduate and graduate teaching. The successful candidate will join an active research program in the Biology Department examining the cellular and molecular basis of behavior using genetic, behavioral and electrophysiological approaches and will be part of a strong research community at Penn in the School of Arts and Sciences and the Professional Schools, including Medicine. The Biology Department is broadly based in animal and plant molecular, cellular, developmental, and evolutionary biology and in ecology.

Applicants are encouraged to email their cover letter, CV, description of research interests and up to three reprints as pdf files to: **PennNeurobiologySearch@sas.upenn.edu** with Neurobiology in the Subject line. Alternatively, these documents may be sent to: **Neurobiology Search, Department of Biology, University of Pennsylvania, Philadelphia, PA 19104-6018**. Applicants at the Assistant Professor level should also arrange for at least three letters of reference to be sent to the email address above (as pdf files) or to the postal address. In addition, a short on-line profile at **https://fusion.sas.upenn.edu/faculty/pos/bio/neuro** must be completed by all applicants.

Review of applicants will begin **November 1, 2007**.

## TENURE-TRACK FACULTY POSITION IN GENOMICS/ SYSTEMS BIOLOGY

The Department of Biology at the University of Pennsylvania is seeking to hire a colleague employing genomic-scale methods to study fundamental problems in any experimental system (animal, fungal, plant, microbial). Areas of interest include, but are not limited to: systems-level studies of functional and/or comparative analysis of gene activity or evolution, cellular, developmental or physiological processes, and computational analysis of biological signals or patterns.

Applicants are expected to have demonstrated excellence and productivity in research, and a desire to teach at the undergraduate and graduate levels. We anticipate that this appointment will be made at the Assistant Professor level, but outstanding senior candidates will be given serious consideration. The University of Pennsylvania encompasses a vibrant and collegial group of genomics researchers; if appropriate, appointment will be made jointly with the Penn Genomics Institute and/or suitable departments within the Schools of Arts and Sciences, Medicine, or Engineering and Applied Sciences. Further information about this search, and the Department of Biology can be found at **www.bio.upenn.edu**.

Applicants are encouraged to email a cover letter, CV, description of research interests and up to three reprints as .pdf files to: **GenomicsBiologySearch@sas.upenn.edu** with Genomics in the subject line. Alternatively, these documents may be sent to: **Genomics Search, Department of Biology, University of Pennsylvania, Philadelphia PA 19104-6018**. Applicants at the Assistant Professor level should also arrange for at least three letters of reference to be sent to the email address above (as .pdf files) or to the postal address. In addition, a short on-line profile at **https://fusion.sas.upenn.edu/faculty/pos/bio/genomics** must be completed by all applicants. Review of applications will begin in late October, and continue until the position is filled.

*The University of Pennsylvania is an Equal Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply.*

USDA ARS Agricultural Research Service
www.ars.usda.gov

*"The premier food and agricultural research agency of USDA"*

## Center Director
## Two Positions – Two Locations

| Eastern Regional Research Center (ERRC) | National Center for Agricultural Utilization Research (NCAUR) |
|---|---|
| **Wyndmoor, Pennsylvania** | **Peoria, Illinois** |

**Senior Executive Service (SES) – Career Reserved**
**ES-1301, 0401-00/00; Salary Range of $111,676 to $168,000**

Applications must be postmarked by **October 15, 2007**.

The ARS is seeking highly qualified candidates for two permanent full-time SES positions. These positions afford the opportunity to:

- Direct an exciting group of scientists working at the leading edge of agricultural science
- Work collaboratively with university and industry
- Oversee facilities with unique physical capabilities and preeminent scientific equipment
- Impact the Nation's leading issues of biofuels, bioproducts and food safety

Join us in enhancing the health and wealth of the Nation and its people. Solving problems, expanding knowledge, delivering answers.

To apply, print a copy of vacancy announcement **ARS:SES:07-04** and/or **ARS:SES:07-05** from the ARS Careers Website at **www.ars.usda.gov/careers** and follow the application directions provided. To have a printed copy mailed or for questions about these positions, call **Deborah Crump** at **(301) 504-1448** or E-Mail: **deborah.crump@ars.usda.gov**. U.S. citizenship is required.

*USDA/ARS is an Equal Opportunity Employer and Provider.*

MichiganTech

## Dean of the College of Sciences and Arts
## Michigan Technological University

Nominations and applications are invited for the position of Dean of the College of Sciences and Arts at Michigan Technological University. We seek a dynamic individual who will move the College forward in achieving the University's goals of becoming a national university of choice and a premier research university of international stature.

The Dean is the chief academic officer of the College and takes the lead in articulating the importance of arts, humanities, computing, mathematics, natural sciences, and social sciences in the general education of all students. The Dean is expected to foster the development and enhancement of innovative programs at both the undergraduate and graduate levels and to encourage increased research and scholarly activity in the college. Required qualifications include distinguished scholarly achievements that warrant appointment as a tenured professor; demonstrated record of academic leadership and fiscal responsibility in higher education; commitment to undergraduate and graduate education; demonstrated ability to attract external funding; and excellent communication and interpersonal skills.

For more information, visit **www.csa.mtu.edu/CSA_Dean_Search**. Application materials should include a cover letter containing a statement of personal qualifications and a description of the candidate's leadership and educational philosophies, current vitae, and the names and contact information of five or more references. Inquiries, nominations, and application materials should be directed to **Professor Mark Gockenbach** at **msgocken@mtu.edu** or **(906)487-2068**. Applications received by **November 1, 2007** will receive full consideration, although review of applications will continue until the position is filled.

*Women and minorities are encouraged to apply. Michigan Technological University is an Equal Opportunity/ Affirmative Action Employer.*

## POSITIONS OPEN

### INTEGRATIVE BIOLOGIST

Eastern Washington University (EWU) Department of Biology invites applications for a full-time, tenure-track **ASSISTANT PROFESSOR** position starting September 2008. The focus of this position is to instruct an integrative sequence in introductory biology for majors and work with other faculty to improve the sequence. The candidate must have a strong commitment to teaching in this area and a research background emphasizing integration across multiple organizational levels within biology. Our Department includes a diverse faculty with over 400 majors and graduate students focusing on ecological, molecular, physiological, and health sciences. EWU is located in Cheney, Washington, near Spokane, Washington, and Coeur D'Alene, Idaho, in the beautiful Northwest. A Ph.D. in biological sciences is required. Please submit letter of application, curriculum vitae, teaching statement, research statement, up to three reprints, copies of transcripts, and have three letters of reference, under separate cover, sent to: **Search Committee, Department of Biology, Eastern Washington University, 258 Science Building, Cheney, WA 99004-2440.** Applications must be postmarked by October 15, 2007. Information about the Department is at **website: http://www.ewu.edu/biology.** *The successful candidate must have the ability to promote and support cultural competency, pass a background check, and show proof of eligibility to work in the U.S. pursuant to U.S. immigration laws. EWU is an Equal Opportunity/Affirmative Action Employer, and application from members of historically underrepresented groups is especially encouraged.*

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### CLIMATE SCIENTIST
**Environmental Studies Department**

The Environmental Studies Department of Macalester College invites applications for a tenure-track Climate Scientist to begin fall 2008. Appointment will be at the **ASSISTANT, ASSOCIATE, or FULL PROFESSOR** rank. Specific areas of climate related interest could include climate dynamics, biosphere-climate interaction (including agricultural systems), biogeochemical cycles, climatology, meteorology, oceanography, geochemistry, and geophysics, among others. The successful candidate is expected to build and maintain an active research program with students. Teaching duties include environmental science, courses in the area of specialty, including climate change, and rotating responsibility for the senior seminar course. Send letter of application, curriculum vitae, statement of teaching philosophy and research plans, and three letters of reference to: **Dr. Dan Hornbach, Chair, Department of Environmental Studies, Macalester College, 1600 Grand Avenue, St. Paul, MN 55105.** Applications received by October 15, 2007, will receive first consideration. More information is at **website: http://www.macalester.edu/provost/positions/index.html.** *Macalester College is an Equal Opportunity/Affirmative Action Employer and strongly encourages applications from women and minorities.*

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The School of Earth and Environmental Science at Washington State University seeks a tenure-track **ASSISTANT PROFESSOR** with expertise in hydroecology. The School will consider applicants from a variety of specialties that address questions linking water and ecological processes. Applicants must have a Ph.D. and provide evidence that they will develop an active, independently funded research program. A commitment to teaching and student training is expected. Applicants should submit: (1) a letter of application outlining teaching and research interests, (2) curriculum vitae, and (3) contact information for four professional references to: **Dr. Richard Gill, Hydroecology Search Chair, SEES, Washington State University, Pullman, WA 99164-2812 U.S.A.; e-mail: rgill@wsu.edu.** Review of applications will begin October 15, 2007. *WSU is an Equal Employment Opportunity/Affirmative Action Employer.*

## POSITIONS OPEN

USDA ARS Agricultural Research Service
www.ars.usda.gov

**RESEARCH MOLECULAR BIOLOGIST,** GS-0401-12/13. The USDA, Agricultural Research Service (ARS), Plant Genetics Research Unit, Columbia, Missouri, is seeking a permanent scientist for research within the ARS facility located at the Donald Danforth Plant Science Center in St. Louis, Missouri. The research focus is soybean seed biology, with emphasis on identifying the genetic, cellular, and molecular mechanisms regulating the accumulation of specific proteins and/or oils. The applicant must apply cutting-edge research to identify the mechanisms that limit accumulation and/or composition of protein and/or oil in seeds, and design strategies to overcome such limitations. The goal of the research includes producing soybean lines with improved seed-based, value-added traits. *U.S. citizenship required.* Salary $63,417 to $98,041. For application procedures and forms, contact **JoAnne Kniptash, telephone: 573-875-5293** or **e-mail: joanne.kniptash@ars.usda.gov,** or visit the ARS **website: http://www.ars.usda.gov/Careers/Careers.htm** and refer to vacancy announcement #ARS-X7W-0327. Applications must be postmarked by October 30, 2007. *USDA/ARS is an Equal Opportunity Provider and Employer.*

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### FACULTY POSITION in MOLECULAR BIOPHYSICS
**Johns Hopkins University School of Medicine**

The Department of Biophysics and Biophysical Chemistry **(website: http://biophysics.med.jhmi.edu)** seeks outstanding candidates for the position of **ASSISTANT PROFESSOR.** Applications are sought in all areas of molecular biophysics and biophysical chemistry, including, but not limited to, enzymology, structural biology, single molecule studies, computational biophysics, biological spectroscopy, and mechanistic biochemistry. Priority will be given to applications received by November 1, 2007. Please submit paper copies of curriculum vitae, a summary of current and proposed research, and arrange to have three letters of recommendation sent to:

**Search Committee**
**Department of Biophysics and Biophysical Chemistry**
**Johns Hopkins University School of Medicine**
**WBSB 713**
**725 North Wolfe Street**
**Baltimore, MD 21205-2185**
**Fax: 410-502-6910**

*The Johns Hopkins University is an Equal Opportunity Employer.*

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The University of Redlands invites applications for a **TENURE-TRACK FACULTY POSITION** in biology. The successful candidate will have appropriate training and expertise to teach animal physiology; responsibilities will include teaching both nonmajors and majors and involving undergraduates in research. A Ph.D. (by September 2008), evidence of excellence in undergraduate teaching, and a commitment to undergraduate research are required. Please send letter of application, curriculum vitae, description of research plans, statement of teaching philosophy with a list of potential course offerings, and arrange for three letters of recommendation to be sent to: **Chair, Search Committee, Department of Biology, University of Redlands, P.O. Box 3080, Redlands, CA 92373-0999.** Applications received by October 26, 2007, are assured full consideration. Located in an ethnically and culturally diverse region midway between Los Angeles and Palm Springs, the University of Redlands **(website: http://www.redlands.edu)** is a private, selective, liberal arts university enrolling approximately 2300 undergraduates in the residential College of Arts and Sciences. *The University of Redlands is an Equal Opportunity Employer. We actively seek applications from members of underrepresented populations.*

## POSITIONS OPEN

The Department of Organismic and Evolutionary Biology invites both nominations and direct applications for the **HRDY VISITING FELLOWSHIP in CONSERVATION BIOLOGY** for the academic year 2008-2009. The Hrdy Visiting Fellowship is available either at the senior faculty level or at the junior (i.e., postdoctoral) level for one or two semesters. Duties will include teaching one course and/or giving lectures in conservation biology, as well as research and collaboration with members of the Harvard community. The Fellowship includes a modest travel stipend. Applicants should contact a faculty sponsor(s), with whom they will collaborate, before applying. Applications should include a cover letter with a statement of intent, curriculum vitae, and representative publications, and applicants should arrange to have three letters of reference sent. Inquiries and applications may be sent either electronically or by paper to **e-mail: kparodi@oeb.harvard.edu** or to:

**Committee for Hrdy Fellowship in Conservation Biology**
**Department of Organismic and Evolutionary Biology**
**Harvard University**
**26 Oxford Street**
**Cambridge, MA 02138**

*Harvard University is an Equal Opportunity Employer.*

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### ASSISTANT or ASSOCIATE PROFESSOR
**(Marine Life Sciences)**

The Graduate School of Oceanography (GSO) of the University of Rhode Island invites applications from outstanding scientists for a calendar-year, tenure-track position with eight months of hard money per year. We are particularly interested in scientists who address one or more interdisciplinary topics in marine life sciences. Special attention will be given to applicants with skills in advanced technologies such as: genomics, proteomics, remote sensing, data assimilation, and numerical modeling. Visit our **website: http://www.uri.edu/human_resources** for full requirements. Review of applications will begin October 12, 2007, and continue until filled. Please send via e-mail or regular post, a letter of application, curriculum vitae, statement of teaching philosophy and research interests, and the names and addresses of four references to **e-mail: marinelifesciencessearch@gso.uri.edu** or to: **Peter C. Cornillon, Search Chair, (Requisition # SCI011842), University of Rhode Island, P.O. Box G, Kingston, RI 02881.** *URI is an Affirmative Action/Equal Employment Opportunity employer and values diversity and also is an NSF ADVANCE institutional transformation university, working to advance the careers of women faculty, especially in the science and engineering disciplines.*

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### CAREER OPPORTUNITY

This unique program offers the candidate with an earned Doctorate in the life sciences the opportunity to obtain the Doctor of Optometry (O.D.) degree in 27 months (beginning in March of each year). Employment opportunities exist in research, education, industry, and private practice. Contact the **Admissions Office, telephone: 800-824-5526** at the **New England College of Optometry, 424 Beacon Street, Boston, MA 02115.** Additional information at **website: http://www.neco.edu, e-mail: admissions@neco.edu.**

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**POSTDOCTORAL FELLOW POSITIONS** available to study the role of membrane-anchored metalloproteinases in development and cancer (e.g., *Cell* **125**:577, 2006 and **114**:33, 2003; *Genes Dev.* **20**:2673, 2006). Strong background in cell or molecular biology required. *U.S. citizens and resident aliens only.* Send curriculum vitae and letters of reference to: **Stephen J. Weiss, M.D., Upjohn Professor of Medicine, Chief, Molecular Medicine and Genetics, University of Michigan, 5000 LSI, 210 Washtenaw, Ann Arbor, MI 48109-0640.**

## POSITIONS OPEN

### ASSISTANT RESEARCH PROFESSOR in HYDROLOGICAL/ECOLOGICAL INFORMATICS
**The University of Arizona**

The Colleges of Agriculture and Life Sciences and Engineering at the University of Arizona in Tucson invite applications for a nontenure-eligible faculty position at the Assistant Research Professor level (100 percent research; academic year appointment) with expertise related to hydrological/ecological informatics. The person in this position will provide technical leadership and oversight of the development of a statewide water informatics system, Arizona Hydrologic Information System (AHIS). AHIS is a critical component of the tri-university Arizona Water Institute. Expertise is required in informatics, design and construction of computer database applications, data sharing systems, web-based access and retrieval systems, and applications of integrating large hydrologic, biological, physical, and social datasets in multiple formats across spatial and temporal scales. Experience working on collaborative, multidisciplinary teams and with applied uses of information systems for research and/or decision making is required. It is desirable that the applicant have one or more degrees in a natural resources related field, significant experience in electronic communications, and a proven track record in grantsmanship.

A full description and application for this position is available at **website: https://www.uacareertrack.com/.** Look for job # 38591. This position will remain open until filled, formal reviews began August 6, 2007.

*The University of Arizona is an Equal Employment Opportunity/Affirmative Action, minorities/women/persons with disabilities/veterans employer.*

Contact: **Jeffrey C. Silvertooth, Chair, Soil, Water and Environmental Science Department, 1177 E. Fourth Street, Shantz 429, Tucson, AZ 85721. E-mail: silver@ag.arizona.edu.**

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### BIOLOGIST/BIOINFORMATICS/PROTEIN STRUCTURE

The Department of Biological Sciences at Marquette University has a tenure-track **ASSISTANT PROFESSOR** position available August 16, 2008. Applicants must have a Ph.D. with postdoctoral experience. The successful candidate is expected to develop an extramurally funded research program that will complement existing areas of research within the Department **(website: http://biology.marquette.edu).** Preference will be given to applicants who can also provide expertise in bioinformatics, genomics or protein structure that enhances ongoing programs campus-wide. Teaching responsibilities include an introductory biology course for undergraduate majors and a graduate course in the candidate's area of expertise each year. Review of applications until the position is filled. Candidates should apply online at **website: http://careers.marquette.edu/applicants/Central?quickFind=51073** Application process requires curriculum vitae, statement of research and teaching interests. Three reference letters are to be sent to: **Dr. Robert Fitts, Chair, Department of Biological Sciences, Marquette University, WLS 112, P.O. Box 1881, Milwaukee, WI 53201-1881.**

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Energy, materials, and food from managed ecosystems: the Energy and Resources Group at University of California, Berkeley, seeks a colleague for a full-time, tenure-track appointment at the **ASSISTANT PROFESSOR** level in the interdisciplinary area of energy, materials, and food from managed ecosystems. The closing date is 1 November 2007. For details, see **website: http://erg.berkeley.edu,** or call **telephone: 510-642-1640.**

## POSITIONS OPEN

### ANIMAL PHYSIOLOGIST, ASSISTANT PROFESSOR, TENURE TRACK
**Academic Year 100 Percent**

The Department of Biology in the College of Science and Health at the University of Wisconsin, La Crosse, invites applications for an academic year, tenure-track position at the level of Assistant Professor. We seek an engaging Teacher and Scholar with a strong commitment to undergraduate education and who can serve as an inspirational mentor and role model for students with diverse career goals and backgrounds. The successful candidate will teach animal physiology or environmental physiology, human anatomy and physiology, and develop a course in her/his area of expertise or participate in teaching in our biology core curriculum. A Ph.D. in a biological science is required. Some previous teaching experience and experience with diversity issues is desirable. The successful candidate will be expected to develop an externally funded research program and direct undergraduate and graduate (M.S.) research. Academic year salary is competitive and commensurate with experience. Start August 28, 2008. Applicants should submit letter of application, curriculum vitae, statements of teaching philosophy and research interests, graduate and undergraduate transcripts, and three letters of recommendation to: **Dr. Mark Sandheinrich, Department of Biology, University of Wisconsin-La Crosse, La Crosse, WI 54601.** Electronic applications can not be accepted and applications must be received by November 15, 2007. *UW, La Crosse, is an Affirmative Action/Equal Opportunity Employer. Women, persons of color, and individuals with a disability are encouraged to apply. If you have a special need/accommodation to aid your participation in our hiring process, please contact Mark Sandheinrich to make appropriate arrangements. Employment will require a criminal background check. A pending criminal charge or conviction will not necessarily disqualify an applicant. In compliance with the Wisconsin Fair Employment Act, UW, La Crosse, does not discriminate on the basis of arrest or conviction record.*

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### SENIOR ASSOCIATE EDITOR
*Cancer Research*

The American Association for Cancer Research (AACR) is seeking a mid-career scientist with a broad-based knowledge of cancer research and related sciences to serve as the full-time Senior Associate Editor for *Cancer Research,* the leading journal in the field. The Senior Associate Editor will help develop content by working with authors and the other journal editors to obtain original research and synoptic articles. This individual will also serve as a principal liaison to the scientific community and will attend meetings and monitor literature to keep current with latest developments to enhance the journal's importance to the research community. The Editor will manage and monitor solicited content, in consultation with the Editor-in-Chief, and interact with peer reviewers, authors, and others.

Requirements: Doctorate and three to five years of postdoctoral research experience, superior verbal and written skills, publications, knowledge of journal publishing and editorial processes, strong organizational skills, and the ability to revise content to improve presentation, we invite you to submit your resume/curriculum vitae to: **Human Resources, P.O. Box 40138, Philadelphia, PA 19106; fax: 215-440-1045; e-mail: humanresources@aacr.org.** *Equal Opportunity Employer.*

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### BIOCHEMISTRY

Illinois Wesleyan invites applications for a **TENURE-TRACK POSITION** in biochemistry. Our American Chemistry Society-certified Chemistry Department seeks candidates who share our enthusiasm for interactive learning and student-faculty research. For a complete position description, qualifications, and application instructions, see our advertisement at **websites: http://www.iwu.edu/~iwujobs** or **http://www.ScienceCareers.org.** Review of applications will begin October 22, 2007, and continue until the position is filled. *Illinois Wesleyan University is an Equal Opportunity Employer.*

# Genetic Analysis: Model Organisms to Human Biology

GSA Genetics Society of America

**GSA MEETING**
**January 5-8, 2008**
**San Diego, California**

**KEYNOTE SPEAKERS:**
- **Andy Fire**
- **Richard Axel**
- **Francis Collins**

Two poster sessions
**PLUS**
**19 additional speakers chosen from abstract submissions!**

Abstract Submission Deadline:
**November 14**
Early Registration Deadline:
**December 3**

| SESSIONS | SPEAKERS |
|---|---|
| **Prokaryotes and Pathogens** | Carol Gross<br>Joe DeRisi, Claire Fraser, Stan Leibler |
| **Chromosomes** | Terry Orr-Weaver<br>Johannes Walter, Tom Petes, Pat Hunt |
| **Chromatin** | Barbara Meyer<br>Rudolf Jaenisch, David Allis, Steve Jacobsen |
| **RNA-Mediated Regulation** | Greg Hannon<br>Rob Martienssen, Meng Chao Yao, David Bartel |
| **Technology** | Allan Bradley<br>Hugo Bellen, Michele Calos, Paul Sternberg |
| **Neurobiology and Behavior** | Cori Bargmann<br>Karl Deisseroth, Gene Robinson, Ulrike Heberlein |
| **Population Genetics** | Trudy MacKay<br>Steve Scherer, Daniel Barbash, Sarah Tishkoff |
| **Ageing** | Dan Gottschling<br>Andy Dillin, Leonard Guarente, Daniel Promislow |
| **Bioengineering** | Chris Somerville<br>Claudia Schmidt-Dannert, Mary Lou Guerinot |

**www.GSA-MODELORGANISMS.org**

## CONFERENCE

ANNOUNCEMENT

The 23nd Annual International Conference on **Soils, Sediments and Water**
October 15-18, 2007

Presented by... University of Massachusetts at Amherst

**SESSIONS**

Analysis • Bioremediation • Biotechnology • Brownfields • Chemical Oxidation • Combining Chemical and Biological Technologies • Environmental Fate • Environmental Forensics • Ethics in Environmental Practice • Gasoline Oxygenates • Heavy Metals • Innovative Technologies • Microbubble Ozone Remediation • Modeling • Perchlorate/MECs • Pesticides • Phytoremediation • Regulatory • Remediation • Risk Assessment • Sediments • Site Assessment • Tungsten • Vapor Intrusion

**WORKSHOPS**

1) Compliant Analysis of Water, Wastes and Related Solid Environmental Samples Using Inductively Coupled Plasma Atomic Emission and Mass Spectrometry; 2) In-Situ Chemical Oxidation Workshop; 3) Theory and Use of Field Portable X-ray Fluorescence for Soil Analysis; 4) The 2007 MCP Audit – A Case Study Approach; 5) "Lies, Damned Lies, and Statistics": Avoiding Pitfalls in Environmental Sampling; 6) Evaluating Monitored Natural Attenuation of MTBE and TBA; 7) Environmental Forensic Techniques for Classic and Emerging Contaminants; 8) Environmental Fate of Hydrocarbons in Soils and Groundwater; 9) In-Situ Thermal Remediation; 10) Applied Chemical Fingerprinting in Environmental Forensics; 11) Utilization of Stable Isotopes in Environmental and Forensic Geochemistry Studies; 12) Professional Ethics, Professional Conduct, and Environmental Professionals; 13) Critical Exposure Pathways; 14) Characterizing PAH Bioavailability in Sediments for Remedial Decision-Making; 15) Theory and Application of Molecular Biological Tools ("MBTs") and Biogeochemistry to Bioremediation Process Monitoring and Monitored Natural Attenuation Programs Environmental; 16) Geochemical Evaluations of Metals in Environmental Media: How to Distinguish Naturally Elevated Metals Concentrations from Site-Related Contamination

**For further Information contact the Conference Directors:**
Paul Kostecki, Ph.D. • Edward Calabrese, Ph.D.
Phone: (413) 545-1239 • www.UmassSoils.com

**Check Our Website for more info**
**www.UMassSoils.com**

## AWARDS

### The Debiopharm Life Sciences Award 2007 in neuroscience goes to Dr Zoltan Nusser !

On August 30, 2007, Dr Zoltan Nusser* from the Institute of Experimental Medicine of the Hungarian Academy of Sciences received the Debiopharm Life Sciences Award for his outstanding research in fundamental and clinical neuroscience.

His work focuses on understanding the sub cellular organisation and function of synapses in the central nervous system and their involvement in neuronal network activities underlying sensory perception. Some of his achievements include the FENS/Boehringer Award; the Hungarian "Akadémiai Prize"; the European Young Investigator Award; the Wellcome Trust International Senior Research Fellowship and the Howard Hughes Medical Institute International Research Scholarship. He has published his research in leading publications including Nature, Neuron and PNAS.

The Award ceremony which took place at the Ecole Polytechnique Fédérale de Lausanne (EPFL) in Switzerland, during the EPFL Life Science Symposium 2007, was funded by Debiopharm S.A. and organised by the EPFL. With this nomination, Dr Nusser and his laboratory received CHF 100'000, a certificate and an etched crystal tribute commemorating this honour.

The objective of the Debiopharm Life Sciences Award is to mentor and motivate young innovative European researchers in the field of life sciences, with a focus this year on neuroscience. Potential candidates for the Award are required to be under the age of 40, with research having therapeutic and industrial potential. Selection criteria include novelty and originality of the work, as well as its importance and significance in connection with targeted therapeutic fields.

**The topic for the Debiopharm Life Sciences Award 2008 is oncology**

EPFL ECOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

DEBIOPHARM LIFE SCIENCES AWARD

* Dr Nusser is Head of the Cellular Neurophysiology Laboratory

## POSITIONS OPEN

### FACULTY POSITIONS in POPULATION AND EVOLUTIONARY ECOLOGY at the ASSISTANT/ASSOCIATE LEVEL

As part of its strategic planning, the newly formed Odum School of Ecology at the University of Georgia anticipates multiple new faculty lines and now seeks to fill two tenure-track positions at the level of Assistant or Associate Professor. One post is in the area of population ecology, with the successful applicant expected to complement our existing strengths in theoretical ecology, disease ecology, spatial ecology, species interactions, or conservation biology. We also invite applications for a position in evolutionary ecology, and seek a candidate who integrates field, experimental, and/or theoretical approaches to investigate questions at the interface of ecology and evolution. Successful applicants will be expected to develop a creative research program capable of attracting extramural funding and demonstrate an interest in teaching at the undergraduate and graduate levels. Applicants should submit curriculum vitae, PDFs of three publications, a cover letter indicating career goals, and brief statements of teaching and research interests. Four letters of reference should also be sent. Applicants for the population ecology position should submit application materials to **e-mail: popecol@ecology.uga.edu,** while evolutionary ecology applications should be sent to **e-mail: evoleco@ecology.uga.edu.** To ensure full consideration, applications should be received by October 12, 2007. Additional information about the positions and Odum School can be found at **website: http://www.ecology.uga.edu** or by e-mailing to **e-mail: ecology@uga.edu.** *The University of Georgia is an Affirmative Action/Equal Opportunity Employer.*

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### TEXAS A&M UNIVERSITY
**Department of Biochemistry and Biophysics**

The Department of Biochemistry and Biophysics at Texas A&M University **(website: http://biochemistry.tamu.edu)** invites applications for **TENURE-TRACK FACULTY POSITIONS** in the areas of biochemistry, biophysics, molecular genetics, or structural biology. At least two positions will be filled. Faculty rank is open and applications from outstanding candidates at all levels are encouraged. In addition to establishing vigorous independent research programs, the successful candidates will teach at the undergraduate and graduate levels. Candidates should submit curriculum vitae, up to three reprints, a description of research plans of up to three pages, and arrange for three professional reference letters to be submitted. All documents can be submitted electronically to **e-mail: tamu@bichsearch.tamu.edu** or in paper form to:

**Biochemistry Search Committee**
**Texas A&M University**
**Department of Biochemistry and Biophysics**
**2128 TAMU**
**College Station, TX 77843-2128**

Review of applicants will begin November 1, 2007, and will continue until the positions are filled. *Texas A&M University is an Equal Opportunity/Affirmative Action Employer that is committed to improving diversity.*

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### POSTDOCTORAL POSITIONS
**Prostate Cancer**

An excellent opportunity for career development to instructor and junior faculty appointment, the position will study the development and growth of prostate cancer using mouse prostate stem cell models. Focus will be on the role of the Pim protein kinase and regulation of TOR. Individuals should have a strong background in transgenic/knockout mouse models and molecular biology/protein chemistry. Forward curriculum vitae and the name of three references to: **Andrew S. Kraft, M.D., Director Hollings Cancer Center, 86 Johnathan Lucas Street, P.O. Box 250955, Charleston, SC 29425. E-mail: hccjobs@musc.edu.** Please reference ad #5001.

## POSITIONS OPEN

### FACULTY POSITION
**Community or Ecosystem Ecology**
**Wichita State University**

The Department of Biological Sciences at Wichita State University (WSU) seeks a Community or Ecosystem Ecologist for a tenure-track position at the rank of **ASSISTANT PROFESSOR.** The successful candidate must have a research focus with a significant field component. We also expect the candidate to make use of the WSU prairie field station for research and teaching activities. An attractive startup package is supported by funding from Kansas NSF Experimental Program to Stimulate Competitive Research. All members of the faculty participate in general biology and nonmajors courses, while offering advanced courses in their discipline. The successful candidate is expected to develop and maintain an extramurally funded research program that trains graduate and undergraduate students. Candidates must hold a Ph.D. or equivalent degree in the life sciences and have postdoctoral experience, good communication skills, and a record of research productivity. Applications must include statements of research and teaching interests, comprehensive curriculum vitae, three sample publications, and contact information for three professional references. We seek applicants who are motivated to work in a collegial atmosphere to foster excellence in teaching and research collaborations with existing faculty and are interested in promoting diversity in higher education. The Department includes core facilities in environmental biology, imaging, and bioinformatics, and maintains an animal care facility and greenhouse. More information about the Department is available at **website: http://www.wichita.edu/biology.** Wichita State University is a metropolitan research-intensive university set in a suburban area of the largest city in Kansas and attracts a diverse student body. Review of complete applications will begin on October 8, 2007, and continue until the position is filled. Send applications to: **Dr. William Hendry, Department of Biological Sciences, Wichita State University, 1845 Fairmount, Wichita, KS 67260-0026.** *Wichita State University is an Equal Opportunity Employer.*

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### POSTDOCTORAL RESEARCH ASSOCIATE

Description: Highly motivated and independent individual to work in the areas of genome instability and repeat expansion diseases **(website: http://ase.tufts.edu/biology/labs/mirkin/).**

Requirements: Successful candidate should have a Ph.D. and a strong background in molecular biology and/or genetics. Experience in studies of DNA replication, recombination, and/or transcription in yeast or mammalian cells would be desirable. Areas of laboratory focus include the mechanisms of the instability of DNA repeats, which are responsible for hereditary disorders in humans, and the role of interplay between DNA replication and transcription in genome organization.

Send a cover letter detailing both your scientific experience and your interest in this position, curriculum vitae, and contact information for three references to:

**Professor Sergei M. Mirkin**
**White Family Chair in Biology**
**Tufts University**
**Biology, Barnum 101B**
**Medford, MA 02155**

or **e-mail: sergei.mirkin@tufts.edu.**

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**ANIMAL CELL BIOLOGIST, ASSISTANT PROFESSOR. Gustavus Adolphus College,** Minnesota. Fall 2008. We seek candidates committed to excellence in teaching at a liberal arts college, to developing an active undergraduate research program, and to successfully working with culturally diverse groups. Teaching and research interests in cell signaling using imaging techniques are preferred. More information at **website: http://www.gustavus.edu/oncampus/humanresources/employment/index.cfm.**

## POSITIONS OPEN

Three **POSTDOCTORAL RESEARCH FELLOWSHIPS** and two **RESEARCH ASSISTANT POSITIONS** are available in the Laboratory of Nanomedicine and Biomaterials at Brigham and Women's Hospital, Harvard Medical School. This multidisciplinary research group is focused on the development of novel nanotechnology based approaches for cancer and cardiovascular therapy. The positions require an extensive expertise in the use of high throughput approaches for the development of drug encapsulated targeted polymeric nanoparticles which will be carried by Ph.D. polymer chemist and chemical engineers; and the in vitro and in vivo evaluation of these formulations in appropriate cell and animal models of diseases by Ph.D. cell biologist, biochemist and pharmacologist candidates with B.S. or M.S. level training and appropriate laboratory experience will be considered for Research Assistant position in these areas.

Applications, including curriculum vitae and bibliography, summary of past accomplishments should be sent to:

**Omid C. Farokhzad, M.D.**
**Assistant Professor of Anesthesia**
**Harvard Medical School**
**Department of Anesthesiology**
**Laboratory of Nanomedicine and Biomaterials**
**Thorn-1305**
**75 Francis Street**
**Boston, MA 02115**
**E-mail: ofarokhzad@zeus.bwh.harvard.edu**

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The Center for the Neurobiology of Aging at the University of Florida has **POSTDOCTORAL FELLOWSHIP POSITIONS** available to work with its faculty in all aspects of brain aging including related neurodegenerative diseases and obesity/metabolic aspects of aging. This NIA funded training program has been successful over the past 15 years in preparing researchers for permanent academic and company positions. Applicants must receive their doctoral degree by the start of the fellowship. Please send curriculum vitae and the names of three references to: **Dr. Philip Scarpace, P.O. Box 100267, University of Florida, Gainesville, FL 32610. E-mail: scarpace@ufl.edu.** *This is an Equal Opportunity Institution.*

## MARKETPLACE


# IDT introduces the miRCat™ Cloning Kit for small RNA discovery

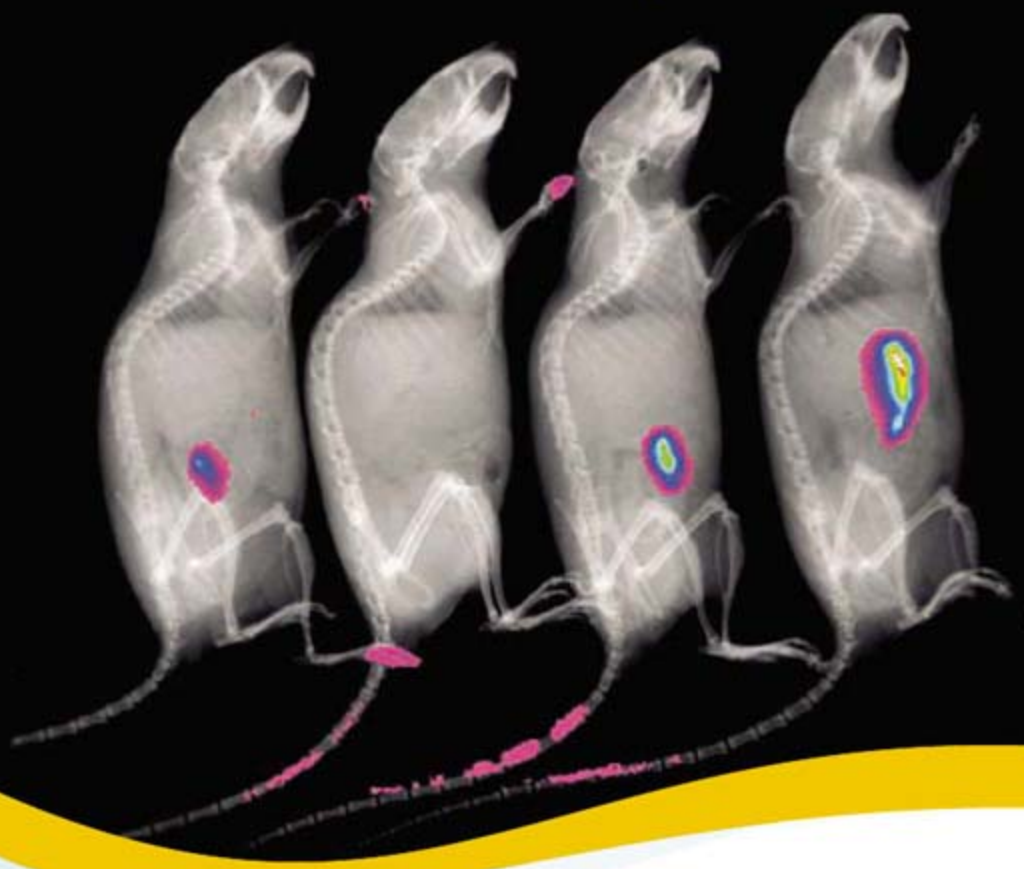
miRCat™ small RNA cloning is based on the pre-activated, adenylated linkering method that has been successfully used in many labs since its development in 2001[1]. miRCat™ permits cloning from any RNA source in any species.

Material sufficient for ten cloning experiments is provided in the miRCat™ Small RNA Cloning Kit, and a detailed technical manual provides instructions for cloning and sequencing small RNAs either as individual clones or as concatamers.

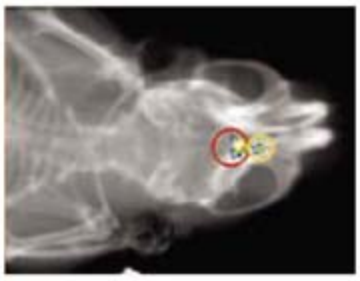
## www.idtdna.com for more miRCat™ information

References
1. Lau NC, LP Lim, EG Wienstein, and DP Bartel 2001 An abundant class of tiny RNAs with probable regulatory roles in Caenorhabditis elegans. Science 294: 858-862.

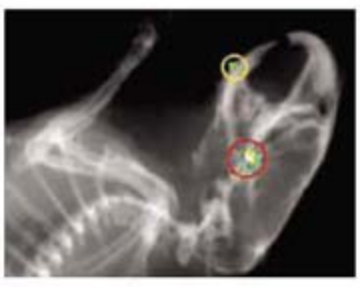
# Powerful, Multi-modal Imaging



## Now so easy everyone is lining up to do it!



Ventral position imaging shows two optical signals generating metastatic lesions located in the cranial region of the mouse.



Subsequent lateral position imaging clearly separates the two lesions to specific jaw and skull locations.

*Images Courtesy Dr. Bohumil, Bednar, Merck Co., Inc.*

## **Kodak** Molecular Imaging Systems

The KODAK In-Vivo Imaging System FX Pro combines high-sensitivity Optical Molecular Imaging and high resolution digital X-ray to deliver precise anatomical localization of molecular and cellular biomarkers.

**New full precision automation makes complex multi-modal imaging protocols easy and repeatable.**

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- Automated imaging chamber enables remote switching between optical, X-ray or radioisotopic imaging without moving the subject

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